Tarceva® (erlotinib) Tablets

NDA 21-743/S-016

Supplemental NDA: First-Line Maintenance Therapy in Patients with Locally Advanced or Metastatic NSCLC

Briefing Document for 16 December 2009 ODAC Meeting

Submission Date: 12 November 2009

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EXECUTIVE SUMMARY

Introduction to Supplemental New Drug Application (sNDA)

The Oncologic Drugs Advisory Committee has been requested to evaluate the Supplemental New Drug Application (sNDA) for Tarceva (erlotinib) tablets administered as a single-agent following 4 cycles of platinum-based chemotherapy for first-line maintenance therapy in patients with locally advanced (stage IIIB, not amenable to chemoradiation) or metastatic non-small cell lung cancer (NSCLC).

The basis of this filing is a global multi-center 889-patient, randomized, double-blind, placebo-controlled phase 3 study SATURN (Study BO18192), which met its co-primary endpoints by demonstrating a statistically significant improvement in investigator-assessed progression-free survival (PFS) for all patients (HR = 0.71, $P < 0.0001$) and for patients with EGFR immunohistochemistry (IHC)-positive tumors (HR = 0.69; $P < 0.0001$). This improvement in PFS translated into a survival improvement (HR = 0.81, $P = 0.0088$).

The safety data from the SATURN study is consistent with the overall Tarceva experience to date. While Tarceva treatment was associated with a higher frequency of adverse events overall, treatment discontinuations for Tarceva-related toxicities were low (2.8% Tarceva vs 0.4% placebo). Importantly, there was no evidence of additional quality of life (QoL) burden for patients treated with Tarceva.

The sNDA, which is seeking full approval for the use of a single daily-dose of Tarceva 150 mg administered orally as first-line NSCLC maintenance therapy following platinum-based chemotherapy doublets, was submitted to the FDA for review on 18 March 2009.

NSCLC First-line Maintenance Therapy

In 2009, approximately 219,440 new lung cancer diagnoses and 159,000 deaths from lung cancer are expected. Lung cancer accounts for about 29% of cancer-related deaths, and NSCLC accounts for 85% to 90% of lung cancers [1, 2].

The current standard of care for first-line treatment of advanced (stage IIIB, not amenable to chemoradiation, or metastatic) NSCLC is 4-6 cycles of a platinum-based chemotherapy doublet, which includes a platinum compound (cisplatin or carboplatin)

combined with another chemotherapy agent (eg, vinorelbine, paclitaxel, docetaxel, gemcitabine, or pemetrexed). These chemotherapy doublets have demonstrated modest improvements in survival and have been associated with improved quality of life [3, 4].

More recently, a study of the addition of the VEGF inhibitor, bevacuzimab, in combination with frontline paclitaxel/carboplatin demonstrated further survival benefit in patients with non-squamous histology. However, an efficacy plateau has been reached with available first-line agents. Despite initial responses or disease stabilization with first-line chemotherapy, patients inevitably progress, have declining performance status, and most will die within a year of their diagnosis. In addition, while approved therapies are available in the second- and third-line setting, approximately 40% of first-line NSCLC patients do not receive second-line therapy, and approximately 45% of second-line patients do not receive third-line therapy [5, 6, 7, 8].

One approach that has been investigated in an attempt to improve patient outcomes in the first-line setting has been to evaluate agents with known efficacy in NSCLC immediately following initial response or disease stabilization with platinum-based chemotherapy to "maintain" the initial benefit from therapy and delay disease progression [8, ,11]. The maintenance approach in NSCLC is possible because of the development of therapies like Tarceva, with a proven efficacy and a tolerable side effect profile. Maintenance therapy as an approach represents an important advance in NSCLC because it increases the number of patients exposed to clinically active therapy without adversely impacting their QoL. The randomized placebo-controlled phase 3 study SATURN discussed in this Briefing Document, adds to the data set supporting first-line maintenance therapy in advanced NSCLC, demonstrating a significant improvement in PFS and overall survival (OS) with the administration of a well-tolerated oral agent, Tarceva.

Tarceva Background

Tarceva (erlotinib) is an approved oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI), available in 25, 100, and 150 mg tablet strengths.

The original NDA for Tarceva tablets was approved on 18 November 2004 for the treatment of NSCLC after failure of at least 1 prior chemotherapy regimen (second/third-line NSCLC). This approval was based on the phase 3, global multi-center, double-blind, placebo-controlled study BR.21, which demonstrated a statistically significant and

clinically meaningful prolongation of survival in patients treated with Tarceva compared with placebo (HR = 0.73, *P* = 0.001), with Tarceva reducing the risk of death by 27% compared with placebo. This survival benefit was seen across patient subgroups. The recommended dose of Tarceva in second/third-line NSCLC is 150 mg administered orally once daily as monotherapy.

Following the review of the original NDA in NSCLC in 2004, OSI was asked to conduct a postapproval commitment study to evaluate the relationship between EGFR protein expression and clinical outcome. In study BR.21, the correlation of EGFR protein expression with clinical outcome was a predefined secondary endpoint, but tissue submission was not mandatory. While there appeared to be a greater clinical benefit with Tarceva in patients whose tumors expressed EGFR (EGFR IHC-positive), a benefit could not be ruled out in patients whose tumors did not express EGFR (EGFR IHC-negative). As the SATURN study was already in the design phase, it was proposed as the primary commitment study to evaluate this relationship, with a co-primary objective of PFS in the overall population and PFS in the EGFR IHC-positive population.

The SATURN study design was discussed with FDA under a Special Protocol Assessment (SPA). Important aspects of the study design and analyses that were agreed to during the SPA process included: the overall design, the chemotherapy regimens to be included as appropriate for first-line therapy, PFS as the primary objective but with the study powered for OS as a secondary objective, the inclusion of a co-primary objective for the EGFR IHC-positive population, the proposed analyses to correlate EGFR IHC status (EGFR positive and negative) with clinical outcome, and the utilization of an independent central radiological review to corroborate the investigators' assessed PFS together with its associated charter, which defined the independent review procedure.

SATURN Study

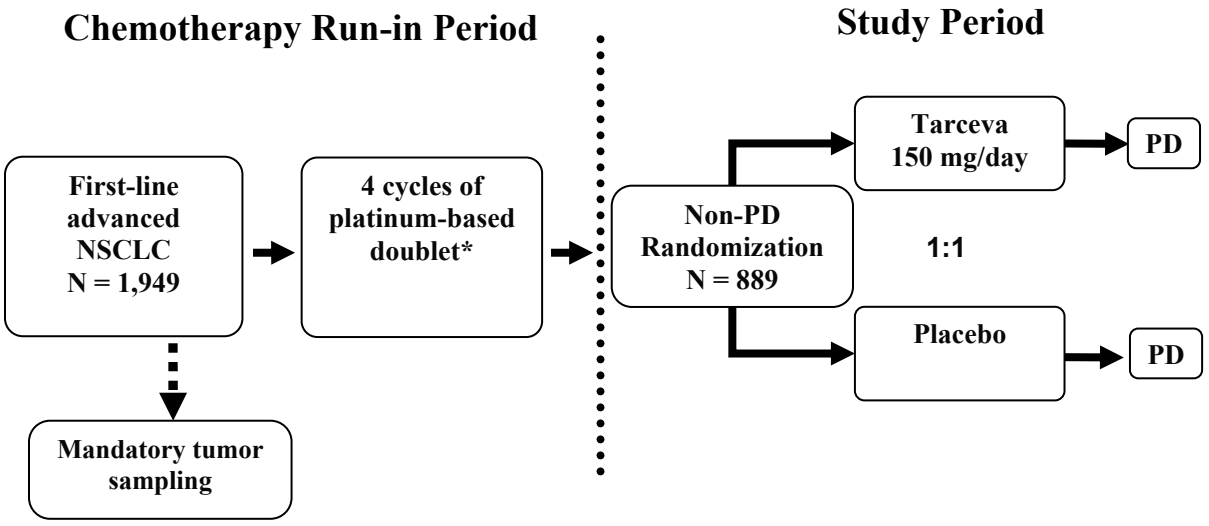
In light of the efficacy of Tarceva in the second/third-line setting of advanced NSCLC, it was hypothesized that administering Tarceva immediately following first-line chemotherapy would improve outcomes in NSCLC patients by maintaining the initial response gained from cytotoxic chemotherapy by delaying progression of disease. In addition, although there was no significant difference in OS for patients receiving Tarceva in combination with chemotherapy in the first-line metastatic setting in two phase 3 studies (TRIBUTE and TALENT), exploratory analyses of data from these

studies suggested increased response duration among patients who continued to receive Tarceva following chemotherapy [12, 13, 14].

Thus, SATURN was designed to investigate the efficacy and safety of Tarceva compared with placebo in the maintenance setting following an initial response or disease stabilization (either complete response [CR], partial response [PR], or stable disease [SD]) from first-line platinum-based chemotherapy in advanced (stage IIIB, not amenable to concurrent chemoradiation, or metastatic) NSCLC.

The primary objective was to evaluate investigator assessed PFS in the overall population, with subsequent central independent radiological review. The co-primary objective to determine PFS in the EGFR IHC-positive population was included to address the postapproval commitment.

Secondary efficacy objectives included comparisons between the 2 treatment arms (Tarceva versus placebo) to evaluate OS in all patients and EGFR IHC-positive population, PFS and OS in the EGFR IHC-negative subgroup, time to symptom progression, safety, population pharmacokinetics, and clinical outcome as it pertained to prespecified exploratory evaluations of tumor tissue, including EGFR and KRAS mutational status and EGFR FISH expression status. Response rates using RECIST criteria and additional quality of life components (including time to deterioration in trial outcome index and time to deterioration in quality of life as well as ad-hoc analyses of the time to pain, analgesics use, cough, and dyspnea) were also evaluated. The study schema is shown below.



Stratification factors:

- **EGFR IHC (+ vs – vs indeterminate)**
- **Stage (IIIB vs IV)**
- **ECOG PS (0 vs 1)**
- **CT regimen (cis/gem vs carbo/doc vs others)**
- **Smoking history (current vs former vs never)**
- **Region**

*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel; cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel; or carboplatin/paclitaxel

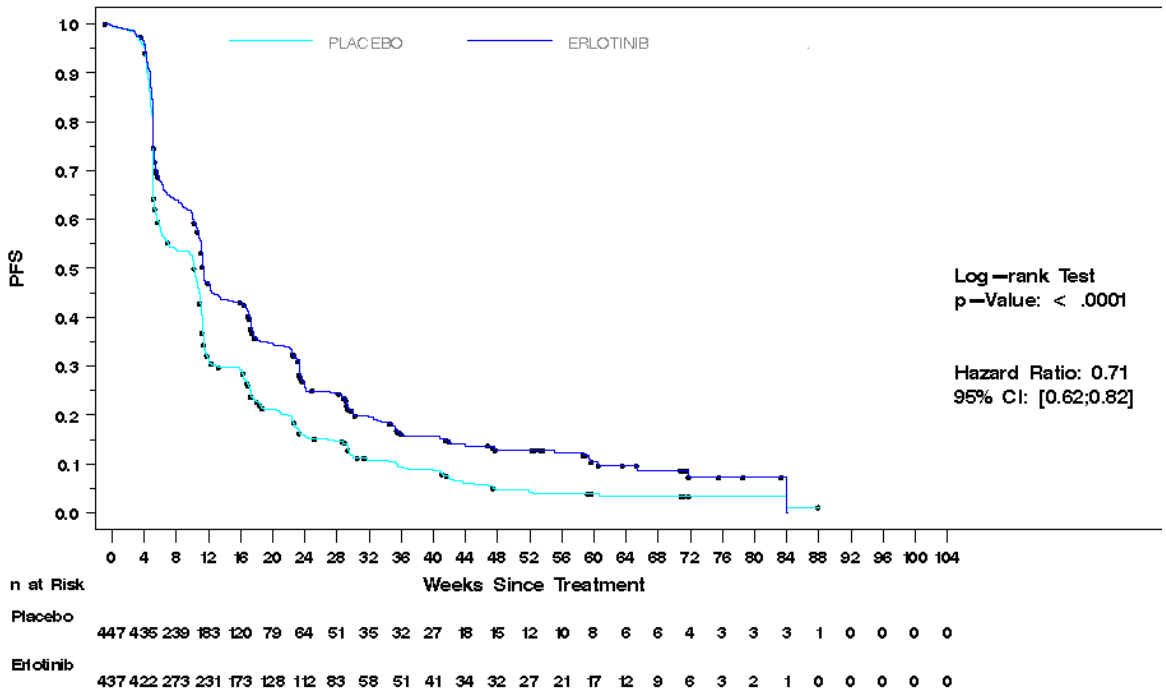
The SATURN study was sponsored by OSI's global development partner F. Hoffmann-La Roche and was conducted in 26 countries across Eastern and Western Europe, North America, South America, and Asia-Pacific in patients with advanced or metastatic NSCLC.

Clinical Efficacy

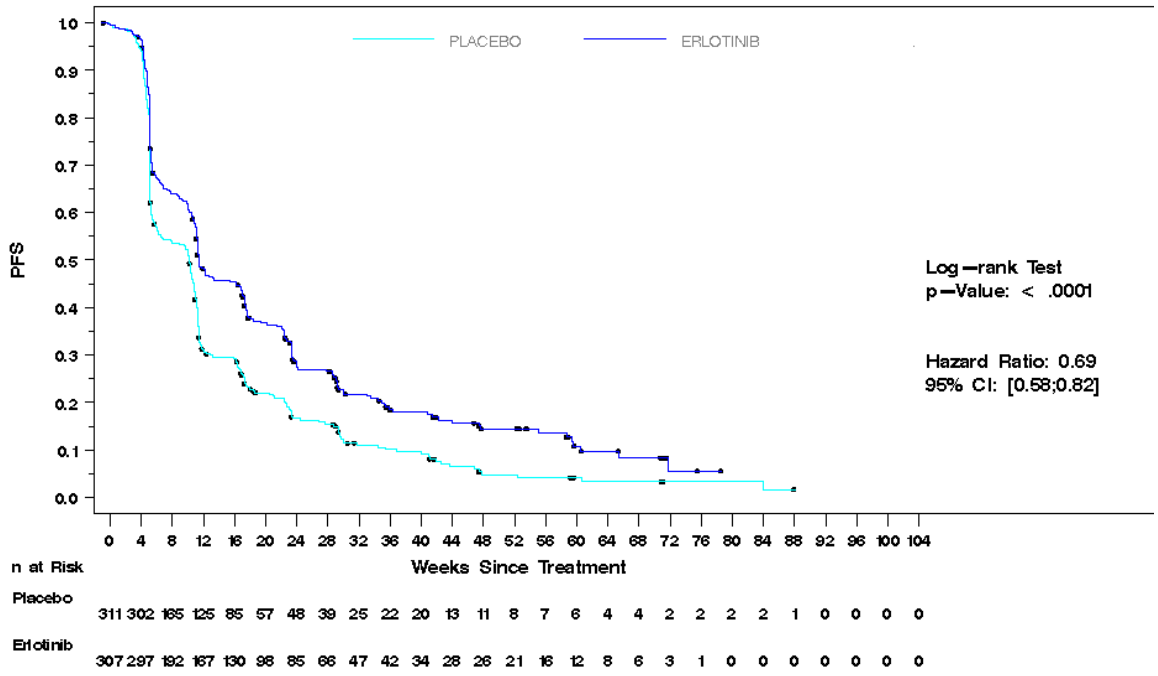
SATURN met its co-primary endpoints by demonstrating a statistically significant improvement in investigator-assessed PFS for all patients (HR = 0.71, $P < 0.0001$) and for patients with EGFR IHC-positive tumors (HR = 0.69; $P < 0.0001$). These investigator-assessed results were corroborated by a central independent radiological review, which demonstrated a high degree of concordance with the investigator assessments. The point estimate of median PFS (12.3 weeks versus 11.1 weeks for both the overall population and EGFR-positive population) does not accurately capture the clinical benefit of Tarceva treatment relative to placebo due to the "stair-step" shape of the Kaplan-Meier (KM) curves corresponding to the disease assessment intervals (most notably, the "pinching" of the curves around the time of the medians). Hazard ratios

better estimate the treatment benefit over the entire study duration. Indeed, once the KM curves separate, they remain separated for the duration of the treatment period. KM curves of PFS for all patients and for the EGFR IHC-positive population are shown below.

Kaplan-Meier Curves of Progression-free Survival in Overall Population (Full Analysis Set)

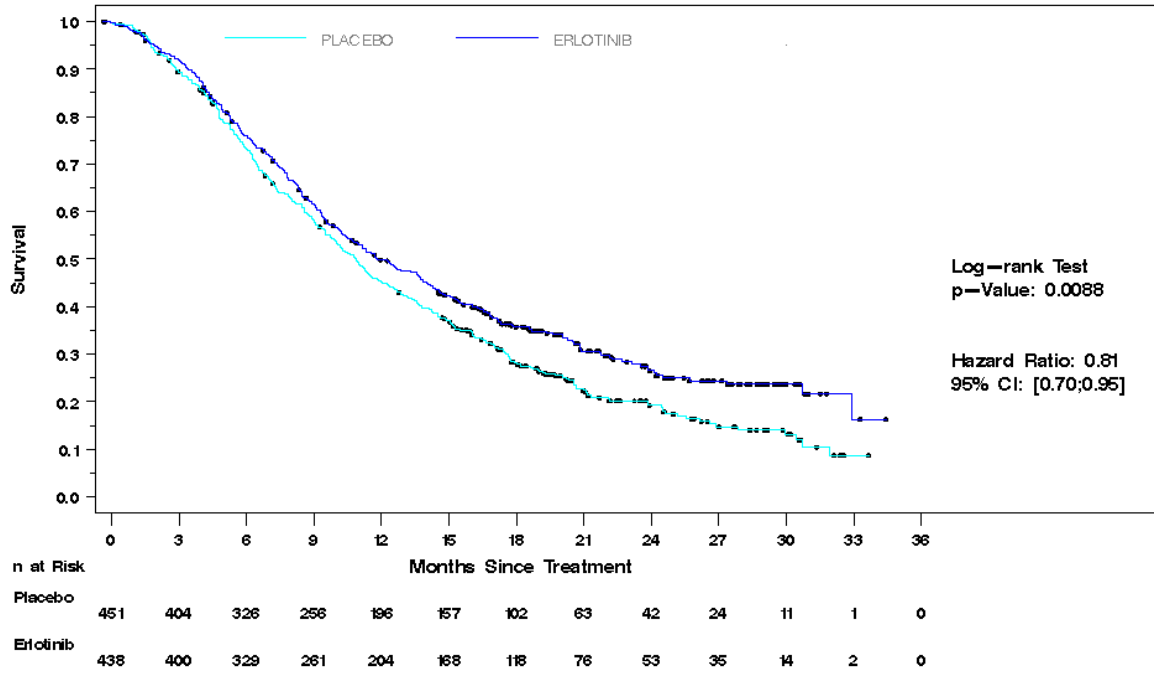


Kaplan-Meier Curves of Progression-free Survival in EGFR IHC-Positive Population

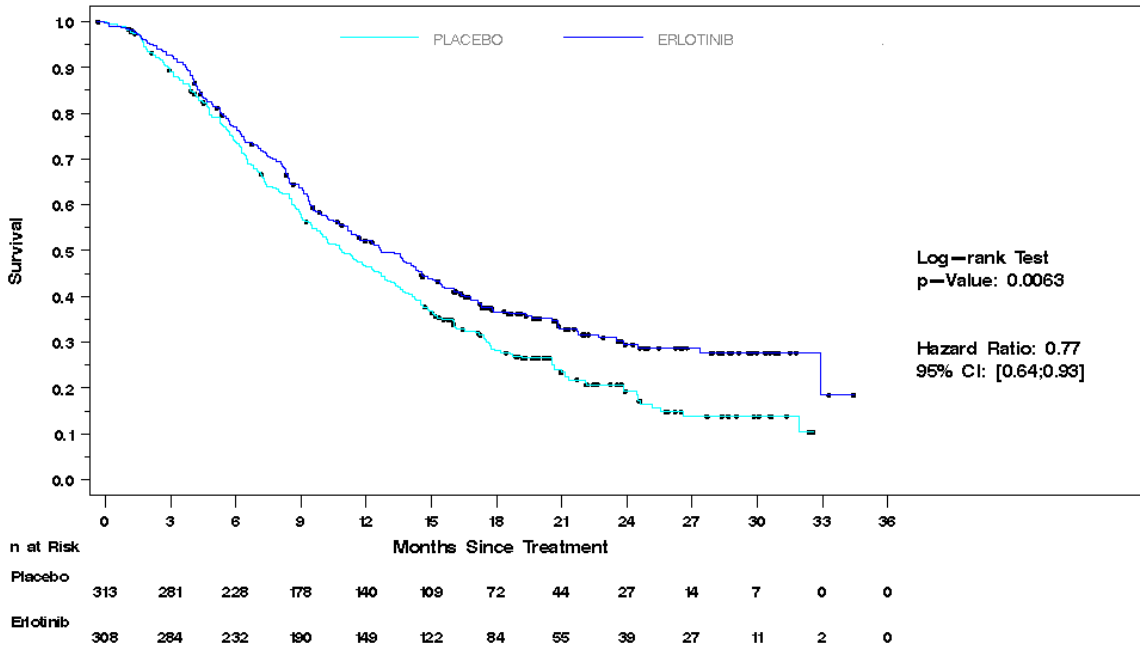


Prolonged PFS correlated with an improvement in OS, a secondary endpoint of the study, in both the overall population (HR = 0.81; *P* = 0.0088) and in EGFR IHC-positive population (HR = 0.77, *P* = 0.0063). The KM curves for OS for both populations are shown below.

Kaplan-Meier Curves of Overall Survival in Overall Population (Full Analysis Set)



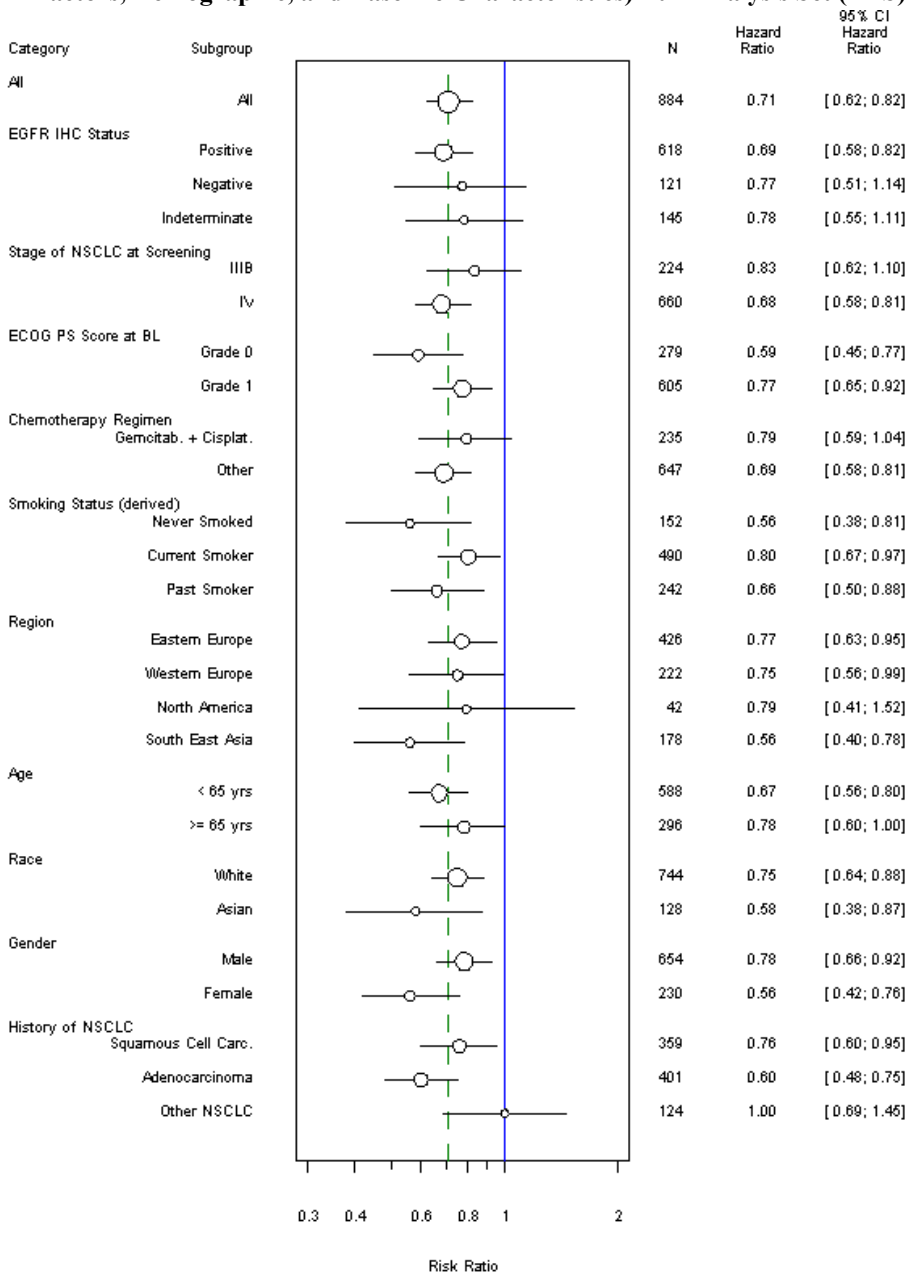
Kaplan-Meier Curves of Overall Survival in EGFR IHC-Positive Population



The improvement in PFS and OS among patients who received Tarceva maintenance therapy was consistent across all clinically relevant phenotypic and biomarker subgroups,

confirming the robustness of these efficacy results. The following Forest plot highlights that all HRs fall at or below 1, demonstrating robust benefit with Tarceva treatment.

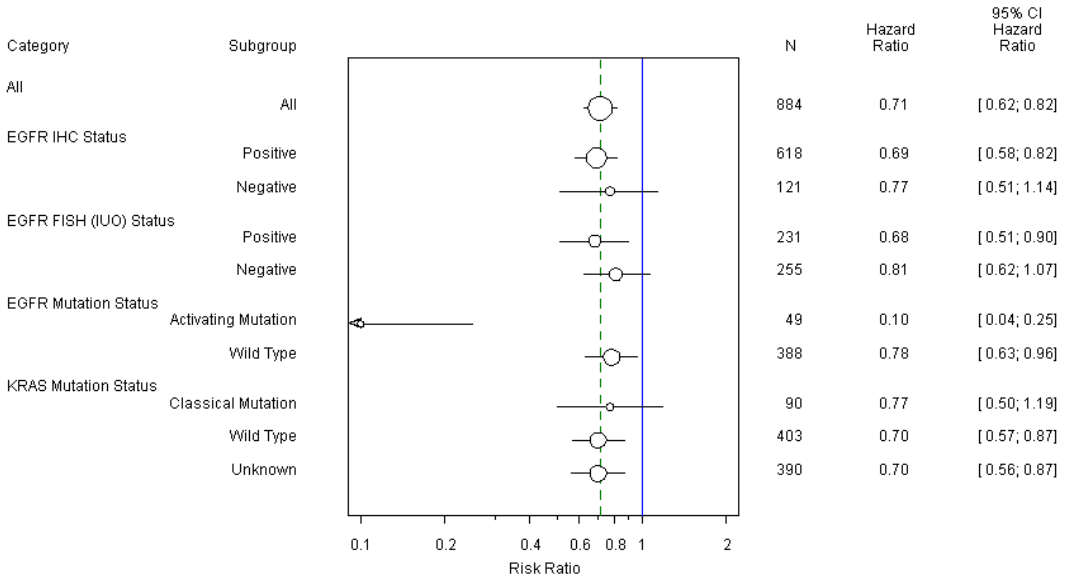
Forest Plot of Hazard Ratios and 95% Confidence Intervals for PFS by Subgroup (Stratification Factors, Demographic, and Baseline Characteristics) Full Analysis Set (FAS)



In addition to EGFR IHC, tumor tissue analyses included evaluation of EGFR FISH, EGFR activating mutation, and KRAS mutations. These biomarker subsets in the context of clinical outcome are shown in the Forest plot below. While EGFR mutation status

predicted for the greatest PFS benefit, patients with EGFR wild type (WT) also had significant benefit. Biomarker subsets by EGFR FISH and KRAS mutation status all had HRs that fell below 1, demonstrating benefit with Tarceva treatment regardless of biomarker expression status.

Forest Plot of Hazard Ratios and 95% Confidence Intervals for PFS by Subgroup (EGFR IHC, EGFR FISH [IUO], KRAS Mutation Status, and EGFR CA-SSR1) Full Analysis Set (FAS)



To evaluate symptom progression and other quality of life measurements, the FACT-L questionnaire was given to patients at baseline and every 6 weeks until Week 48 (or disease progression) and every 12 weeks after Week 48. The time to symptom progression was similar in both treatment groups (HR = 0.91, 95% CI 0.74 to 1.12, *P* = 0.3787).

Clinical Safety

In the SATURN study, Tarceva was administered at 150 mg orally once daily on a continuous basis. Tarceva was well tolerated as evidenced by only 11% of patients requiring a dose reduction to 100 mg once daily from 150 mg and less than 1% requiring a dose reduction to 50 mg once daily. Only 6% of patients receiving Tarceva required a dose interruption for greater than 1 week, and only 4.6% of patients required discontinuation due to adverse events regardless of causality.

Rash and diarrhea were the most common adverse events, consistent with the known safety profile of Tarceva. Forty-nine percent of patients experienced any grade of rash and 20% of patients experienced any grade of diarrhea. Few patients had rash or diarrhea of grade 3 severity (6% and 2%, respectively), and there were no cases of grade 4 rash or diarrhea. Three patients in the Tarceva group developed interstitial lung disease-like conditions during the study. One of these patients died, but possible relatedness to Tarceva treatment was confounded by progressive disease.

The safety profile observed in the SATURN study was consistent with that observed in previous clinical studies of single-agent Tarceva in NSCLC and/or during postmarketing surveillance and as currently described in the Tarceva prescribing information (see **Section 6.1**. There were no new or unexpected safety signals.

Summary of Risk/Benefit Evaluation

Although new chemotherapy and targeted agents have improved the average duration of survival among patients with NSCLC, these improvements have come in small increments of 1-2 months per advance. The applicability of these advances has been limited by treatment constraints due to tolerability, histology, and access to care. Maintenance therapy after first-line chemotherapy represents the most recent advance in the treatment of NSCLC, which has been possible because of the development of therapies such as Tarceva, with proven efficacy and a tolerable side effect profile. This approach is important because it maximizes the number of patients exposed to active therapy by offering treatment early.

Advanced NSCLC patients who received single-agent Tarceva as first-line maintenance therapy had a statistically significant prolonged time to disease progression and a decreased risk of death when compared with patients who received placebo. The SATURN results were consistent across multiple clinically relevant phenotypic and biomarker subgroups. There were no safety signals observed in this population of patients that are not already described in the Tarceva package insert (see **Section 6.1**).

Tarceva is a convenient, oral, non-chemotherapy therapeutic option with manageable side effects that provides an important new therapeutic option for physicians and patients in this setting.

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1 OVERVIEW OF THE FIRST-LINE NSCLC MAINTENANCE SETTING

In 2009, approximately 219,440 new lung cancer diagnoses and 159,000 deaths from lung cancer are expected. Lung cancer accounts for about 29% of cancer-related deaths, and NSCLC accounts for 85% to 90% of lung cancers. The survival rates are generally poor for patients with NSCLC, with an overall 5-year relative rate between 1999 and 2005 of 18.0%. Of the NSCLC diagnosed between 1999 and 2005, 53% of patients presented with cancer that had spread distantly, 22% had regional spread, and only 16% had localized cancer. Late diagnoses are associated with lower survival rates, with a 5-year survival rate of less than 4% when the cancer is diagnosed after it metastasizes [1, 2].

The treatment paradigm for NSCLC is determined by disease stage. Surgery continues to be the mainstay of treatment for early-stage and localized disease, although more recently adjuvant chemotherapy has demonstrated benefit in some patient subsets. Concurrent chemoradiation is the preferred option for patients with locally advanced disease that is not amenable to surgical resection and chemotherapy is the preferred option with palliative radiotherapy when appropriate for patients with advanced stage disease. Approximately 70% of patients with NSCLC present at an advanced stage, including patients with metastatic disease and those with locally advanced disease not amenable to chemoradiation [15].

The diagnosis of advanced NSCLC is devastating for patients and their families. While first-line platinum based chemotherapy has improved survival and quality of life for these patients, this therapy is not curative and many rapidly progress despite initial benefit. Although second- and third-line therapies have been shown to improve survival, approximately 40% of first-line NSCLC patients do not receive second-line therapy, and approximately 45% of second-line patients do not receive third-line therapy [5, 6, 7, 8]. Many patients inevitably are not able to receive such therapies due to declining performance status [8, 16].

The current standard of care for first-line treatment of advanced NSCLC is 4-6 cycles of a platinum-based chemotherapy doublet, which includes a platinum compound (cisplatin or carboplatin) combined with another chemotherapy agent (eg, vinorelbine, paclitaxel, docetaxel, gemcitabine, or pemetrexed) [17]. These chemotherapy doublets have

demonstrated modest improvements in survival and have been associated with improved quality of life. More recently the addition of the VEGF inhibitor, bevacizumab, in combination with frontline paclitaxel/carboplatin has demonstrated further survival benefit in patients with non-squamous histology [18]. However, an efficacy plateau has been reached with available first-line agents. Despite initial responses or disease stabilization with first-line chemotherapy, patients inevitably progress, have declining performance status, and most will die within a year of their diagnosis. Thus, new approaches are required to improve outcome in this devastating disease.

One such approach has been to evaluate agents with known efficacy in NSCLC in the first-line setting after initial response or disease stabilization with platinum-based chemotherapy to "maintain" the initial benefit from therapy and delay disease progression [8, 9, 10, 11]. A number of studies have evaluated the benefit of greater than 4-6 cycles of platinum-based chemotherapy in this setting; however, these studies did not demonstrate survival benefit and resulted in increasing toxicity [4]. Frequently, the cumulative toxicities of first-line platinum-based chemotherapy limit the ability to administer more than 4 cycles of therapy, thus a more recent approach has been to investigate monotherapy in this setting to minimize toxicity while attempting to still offer clinical benefit in delaying progression and improving survival. The taxane docetaxel (Taxotere®) was investigated in this setting and administered (either immediately or delayed until progression) after 4 cycles of platinum-based therapy [5]. The study demonstrated a significant improvement in PFS for patients receiving docetaxel immediately, but was not powered to demonstrate significant improvement in OS. It is notable that fewer than 40% of patients randomized to the delayed arm actually received docetaxel. Pemetrexed (Alimta®), the multi-targeted anti-folate, was recently approved in the first-line maintenance setting in non-progressing patients after 4 cycles of platinum-based chemotherapy. Although demonstrating both an improvement in PFS and OS, its benefit was limited to patients with non-squamous histology.

The randomized, placebo-controlled phase 3 study SATURN discussed in this Briefing Document, adds to the data set supporting first-line maintenance therapy in advanced NSCLC, demonstrating a significant improvement in PFS and OS with the administration of an oral agent, Tarceva. Both the pemetrexed and Tarceva maintenance studies are important trials that demonstrate the ability to improve on outcomes in the first-line setting by shifting the current treatment paradigm. For a heterogeneous patient

population such as that existing in advanced NSCLC, having additional treatment options for physicians and their patients is important for maximizing outcomes.

2 OVERVIEW OF THE DEVELOPMENT PLAN

2.1 Tarceva

Tarceva is an orally-available human epidermal growth factor receptor (EGFR) type 1 (HER1, also known as EGFR or erbB1) tyrosine kinase inhibitor (TKI). HER1/EGFR plays a critical role in many cell-signaling pathways that influence cell division, apoptosis, motility, and adhesion [19]. Ligand binding to the EGFR initiates a cascade of events, with signal transduction culminating in nuclear gene activation, critical in both tumorigenesis and tumor growth. EGFR and its ligands are overexpressed or involved in autocrine growth loops in a number of tumor types including NSCLC [20, 21, 22].

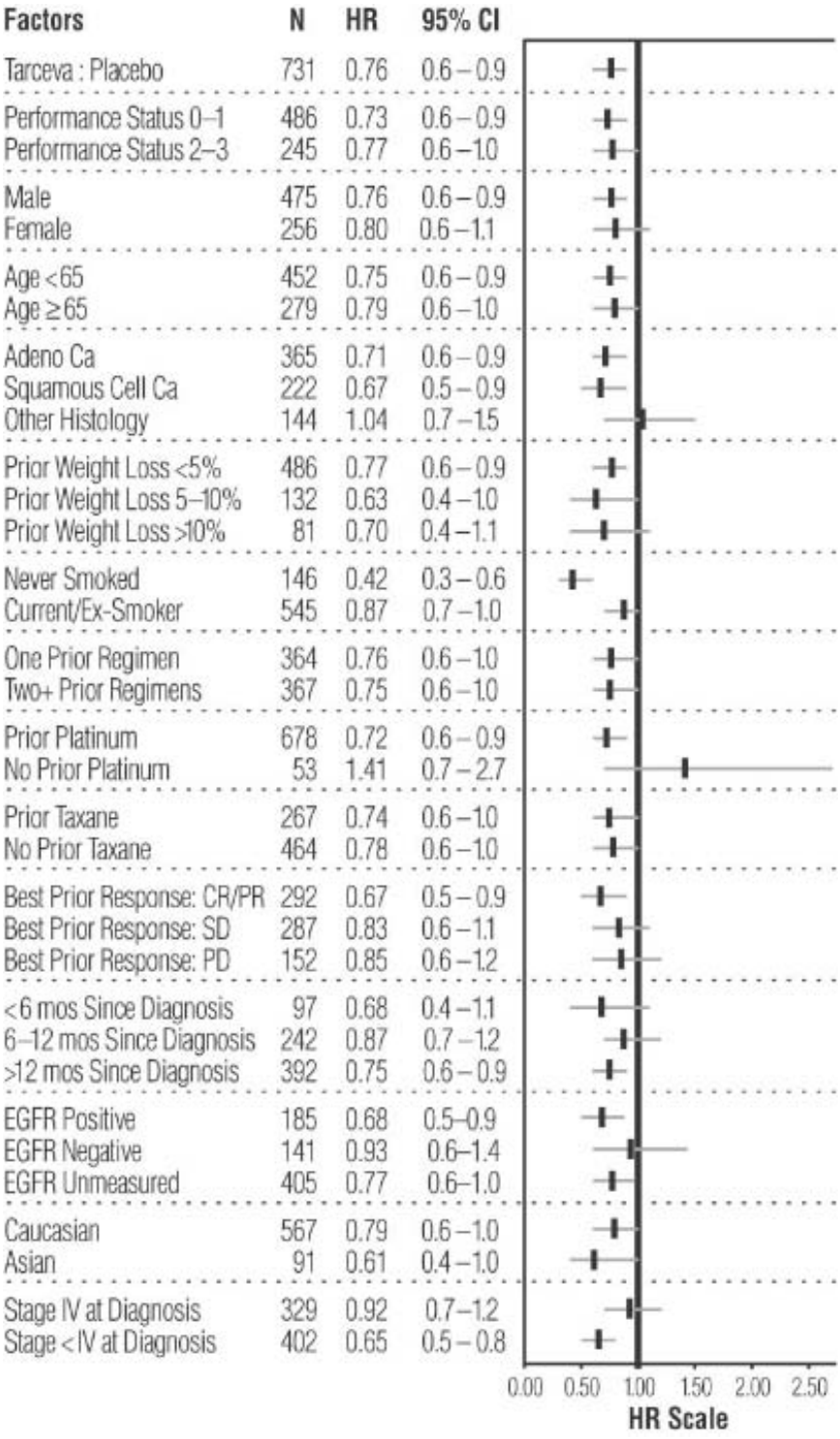
Tarceva inhibits human EGFR tyrosine kinase with an IC_{50} of 2 nM (0.79 ng/mL) in an in vitro enzyme assay and reduces EGFR autophosphorylation in intact tumor cells with an IC_{50} of 20 nM (7.9 ng/mL). EGFR is overexpressed in a significant proportion of epithelium-derived carcinomas. Tarceva inhibits the epidermal growth factor (EGF)-dependent proliferation of cells at nanomolar concentrations and blocks cell cycle progression at the G1 phase.

2.1.1 Current Indications

Tarceva (erlotinib) received full approval by the FDA on 18 November 2004 for the treatment of patients with locally advanced or metastatic NSCLC after failure of at least 1 prior chemotherapy regimen (second/third-line NSCLC). The approval was based on positive data from study BR.21 (conducted by the National Cancer Institute of Canada Clinical Trials Group [NCIC CTG] and OSI Pharmaceuticals, Inc.), a randomized, double-blinded, placebo-controlled, global, 731-patient phase 3 study of single-agent Tarceva 150 mg oral daily and best supportive care versus placebo and best supportive care [23]. In this study, the HR for death in the Tarceva arm relative to the placebo arm was 0.73 ($P = 0.001$). The actuarial 12-month survival rates were 31% and 22%, respectively, in favor of Tarceva treatment (see information in Package Insert, **Section 6.1**). A series of subsets of patients were examined in exploratory univariate analyses, as shown in **Figure 2-1**. The effect of Tarceva on survival was similar across most subsets.

An apparently larger effect, however, was observed in 2 subsets: patients with EGFR positive tumors and patients who never smoked.

Figure 2-1 BR.21 Survival Hazard Ratio (HR) (TARCEVA : Placebo) in Subgroups



Although study BR.21 evaluated the relationship between tumor EGFR protein expression status by IHC and survival outcome, there were limited tumor samples for analysis, as the collection of tumor tissue was voluntary in this study. The original dataset submitted with the NDA contained tumor tissue that was evaluable for analysis of EGFR protein expression by IHC for 33% of the patients. A positive EGFR expression status was defined as having at least 10% of cells staining for EGFR in contrast to the 1% cut-off specified in the EGFR pharmDx™ kit instructions. While the available results suggested a greater benefit of Tarceva in patients whose tumors were EGFR IHC-positive (HR = 0.65), benefit could not be ruled out in the IHC-negative population (HR = 1.01). These data were subsequently updated with additional tumor collection and analysis, which resulted in the EGFR status being determined for 45% of patients. This additional analysis supported the conclusions of the initial analysis (HR = 0.68 for patients with EGFR IHC-positive tumors and HR = 0.93 for patients with IHC-negative tumors) and the prescribing information was updated as a result with the information shown in **Figure 2-1**. Given the limitations of this dataset however, the approval of Tarceva in this setting was not limited to EGFR IHC-positive patients.

Tarceva was also approved on 2 November 2005 for use in combination with gemcitabine in the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer. This indication is based on data from study PA.3, a randomized, placebo-controlled, phase 3 study of Tarceva that showed a survival advantage of Tarceva at a dose of 100 mg daily given in combination with gemcitabine versus gemcitabine alone. More information on this indication is provided in the Package Insert provided in **Section 6.1**.

2.1.2 Regulatory Discussion of the SATURN Study

As mentioned in **Section 2.1.1**, in study BR.21, the relationship between EGFR protein expression as measured by IHC and survival outcome was not conclusive, in part because of the low number of tissue samples available for analysis, as tissue collection was not mandatory in the study.

In light of these EGFR data, the Agency requested a postapproval commitment for the original Tarceva NDA to further evaluate, via mandatory tissue collection, the relationship between EGFR expression and clinical outcome. As the SATURN study was in the design phase at this time (September 2004), it was proposed that outcome in the EGFR IHC-positive patient population be a co-primary objective and this was agreed

to as the primary postapproval commitment to evaluate this relationship, and this commitment was included in the NDA approval letter (November 2004).

More detailed feedback from the Agency on the overall study design was received in December 2004 via a Type B Clinical meeting. However, the Agency asked for the study to be subsequently formally reviewed under the Special Protocol Assessment (SPA) process, and a SPA that incorporated the Agency feedback from the December 2004 meeting with FDA was filed in March 2005.

Important aspects of the study design and analyses that were agreed to during the SPA process included: (1) the overall design, (2) the chemotherapy regimens to be included as appropriate for first-line therapy, (3) PFS as the primary endpoint but with the study powered for OS, (4) the inclusion of a co-primary endpoint for the EGFR IHC-positive population, (5) the proposed analyses to correlate EGFR IHC status (EGFR IHC-positive and negative) with clinical outcome, (6) the secondary endpoints, (7) the use of the investigator assessment of progression for the primary endpoint with corroboration from an independent central radiology review, and (7) the charter for the central review, which defined the independent review process.

2.1.3 Clinical Background for SATURN Study

Given the efficacy of Tarceva in the second/third-line setting of advanced NSCLC (BR.21), it was hypothesized that administering Tarceva immediately following first-line chemotherapy would improve outcomes in NSCLC patients by maintaining the initial response gained from cytotoxic chemotherapy and delaying progression of disease.

In addition, consideration was given to results of earlier studies with Tarceva in the first-line setting. In the phase 3, placebo-controlled TALENT study, patients with previously untreated advanced NSCLC were randomized to receive Tarceva 150 mg daily or placebo with 6 cycles of gemcitabine and cisplatin followed by Tarceva/placebo monotherapy. Although there was no significant difference in OS for Tarceva demonstrated in this study, further exploratory analyses of the data from this study showed that patients who continued treatment with Tarceva for more than 150 days following benefit from 6-cycles of chemotherapy showed increased response duration compared with placebo [14]. These data indicated a possible benefit of single-agent Tarceva as a maintenance therapy following chemotherapy as first-line treatment for advanced NSCLC. In another phase 3 study of Tarceva given in combination with

chemotherapy in the first line setting (TRIBUTE), patients were randomly assigned to receive carboplatin and paclitaxel plus Tarceva or placebo followed by maintenance Tarceva/placebo. This study also did not meet its primary end point of improving OS, but exploratory analyses again showed that patients who continued to receive Tarceva monotherapy following chemotherapy had improved survival [13, 14].

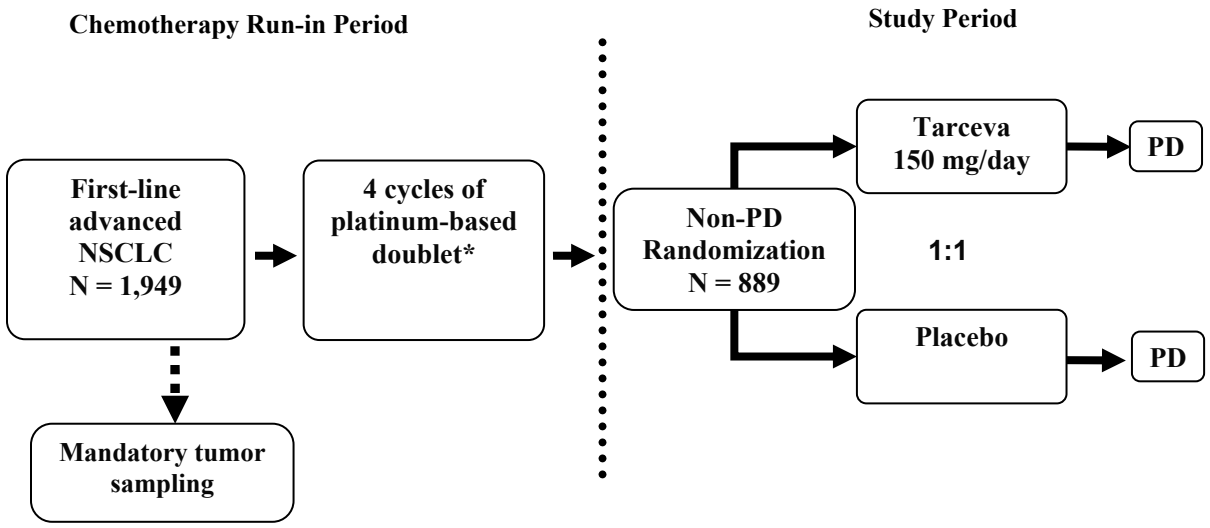
The SATURN study was designed to investigate the efficacy and safety of Tarceva in the maintenance setting following benefit (response or stable disease) from 4 cycles of first-line platinum-based doublet chemotherapy in advanced NSCLC. To address the postapproval commitment, the study was also designed to evaluate the relationship between EGFR expression and clinical outcome.

3 SATURN STUDY

3.1 Overview of Design

SATURN was a global, multi-center, randomized, double-blind, placebo-controlled phase 3 study. The study comprised 2 periods: the chemotherapy run-in period during which patients were receiving first-line platinum-based doublet chemotherapy, followed by the study period, during which patients received blinded Tarceva/placebo, as shown in **Figure 3-1**.

Figure 3-1: SATURN Study Schema



Stratification factors:

- **EGFR IHC (+ vs – vs indeterminate)**
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- **Smoking history (current vs former vs never)**
- **Region**

*Cisplatin/paclitaxel; cisplatin/gemcitabine; cisplatin/docetaxel; cisplatin/vinorelbine; carboplatin/gemcitabine; carboplatin/docetaxel; or carboplatin/paclitaxel

Key eligibility criteria included the following.

- Histologically documented, locally advanced or recurrent (Stage IIIB and not amenable for combined modality treatment) or metastatic (Stage IV) NSCLC before chemotherapy;
- Mandatory submission of formalin-fixed, paraffin-embedded tumor tissue samples within 3 weeks of starting chemotherapy;
- Completion of 4 cycles of an acceptable, standard, platinum-based chemotherapy doublet without progression (ie, CR, PR, or SD);
- ECOG Performance Status (PS) of 0 – 1 before and after chemotherapy; and
- Adequate hematopoietic and end-organ function.

The objectives of the study were as follows.

Primary Objective: To determine if the administration of Tarceva after standard platinum-based chemotherapy in the treatment of NSCLC results in improved PFS when compared with placebo:

1. In all patients, and
2. In patients who are EGFR immunohistochemistry (IHC) positive.

Secondary Objectives

1. To compare OS between the treatment arms for all patients and for patients who are EGFR IHC-positive;
2. To compare PFS between the treatment arms in patients who are EGFR IHC-negative;
3. To compare OS between the 2 treatment arms for patients who are EGFR IHC-negative;
4. To perform exploratory evaluations of tumor-tissue for biological or genomic determinants of outcome, including EGFR and KRAS mutational status and EGFR copy number (FISH);
5. To compare time to symptom progression between the 2 treatment arms;
6. To evaluate the safety profile of administering Tarceva after a standard platinum-based chemotherapy in the treatment of NSCLC; and
7. To investigate by a population analysis approach the pharmacokinetics of Tarceva in the target population.

Response rates using RECIST criteria and additional analyses of quality of life components (including time to deterioration in trial outcome index and time to deterioration of QOL) were also predefined analyses. Ad hoc analyses of time to pain, analgesics use, cough, and dyspnea were also performed.

Because of the importance of the biomarker evaluations in this study, all patients were required to provide a tumor tissue sample within 3 weeks of starting chemotherapy. They were then required to successfully complete 4 cycles of a standard platinum-based chemotherapy combination in the absence of unacceptable toxicity and/or disease progression (ie, complete response [CR], partial response [PR], or stable disease [SD]). Eligible patients were randomized 21 days after completion of the last cycle of chemotherapy administration and study drug administration was initiated within 7 days of randomization.

To allow the investigator to have the option of selecting the best second- or third-line treatment, unblinding of patients after progressive disease (PD) was possible in exceptional cases if, in the opinion of the investigator, the use of an EGFR-TKI was the only option in this setting for the patient.

An independent Data Safety Monitoring Board (DSMB) was set up to perform regular 3-monthly reviews of safety data during the course of the study. In addition, the DSMB was to review safety and efficacy data at the time of the interim analysis that was performed when approximately 50% of the required number of PFS events had occurred. Upon review of the data from the interim analysis, the DSMB found no unexpected safety concerns and recommended the study continue as planned.

3.1.1 Dose Selection

The selection of the 150 mg/day dose of Tarceva for SATURN was based on the approved single-agent commercial dose for Tarceva in second/third-line NSCLC.

3.1.2 Safety Assessment

Clinical safety assessments performed throughout the study included physical examination (with description and quantification of any lung symptoms if present), 12-lead ECG, adverse events (AEs), and serious adverse events (SAEs) reported and severity graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE, version 3.0). If clinically indicated, an ophthalmologic examination was to be performed. Laboratory (blood chemistry and hematology) assessments were performed locally and severity was also graded using NCI-CTCAE version 3.0.

3.1.3 Statistical Design

SATURN was designed as a superiority trial. Two primary analyses were performed:

1. PFS based on the full analysis set (FAS) in the overall, randomized population; and
2. PFS based on the subgroup of patients with EGFR IHC-positive tumors.

The study was to be declared positive if either or both of the primary analyses were statistically significant at their prespecified significance levels. For the analysis of the overall population, the significance level was 3% (2-sided), using an unstratified log-rank test. For the analysis of the EGFR IHC-positive population the significance level was 2%, using an unstratified log-rank test. Overall, the study had a 5% significance level. Following the interim analysis, the significance levels to be used for the final analysis were 0.02934 for the FAS and 0.01967 for the EGFR positive subset.

There was a protocol-defined hierarchy of testing for the secondary parameters, in which overall survival was considered the most important secondary endpoint. For the secondary parameters and exploratory analyses further tests between the 2 treatment arms were performed. All tests were 2-sided at an alpha-level of 5%.

Stratification factors included EGFR IHC status, stage of disease of NSCLC at screening, ECOG PS, chemotherapy regimen, smoking status, and geographic region.

3.1.3.1 Planned Sample Size

The study was powered to perform two primary analyses, to compare PFS between the 2 treatment arms in all patients and in patients who had EGFR IHC-positive tumors. The required number of events and the related number of patients were calculated based on the analysis of PFS for all patients.

In order to detect a 25% improvement in the median PFS with Tarceva compared with placebo (HR = 0.80) with 80% power at a 2-sided 3% significance level, 731 events (progression or death) were required. Assuming 18 months accrual, 6 months follow-up of last patient, and a 5% dropout rate over 2 years, 427 randomized patients per arm were required. It was expected that approximately 2000 patients would need to be screened.

Based on study BR.21, approximately 50% of patients were expected to have EGFR IHC-positive tumors. This estimate would lead to approximately 215 randomized patients per arm for testing the treatment difference in PFS for EGFR IHC-positive population. The HR was expected to be lower in this subset of patients. A test of the difference in PFS for EGFR IHC-positive population at a 2-sided significance level of 2% would have 85% power to detect a HR of 0.7 (360 events expected) and 66% power for a HR of 0.75 (365 events expected).

Additional considerations were given to the first secondary endpoint of OS, assuming a 10-month median survival in the placebo arm. In order to detect a 25% improvement in the median survival with Tarceva compared with placebo (HR = 0.8) with 80% power at a 2-sided 5% significance level, 641 events (deaths) were required. Assuming 18 months accrual, 427 randomized patients per arm, and 5% dropout over 2 years, 641 events were expected to occur at approximately 15 months after the last patient was randomized.

The primary data analysis was conducted after 749 events of progression or death, 400 in the Tarceva group and 349 in the placebo group (data cut-off of 17 May 2008). At that

time, survival data were not yet mature. The data cut-off date for the overall survival analysis was 1 year later (17 May 2009), at which time a total of 648 events of death occurred, 298 (68%) on Tarceva and 350 (78%) on placebo.

Although in the SATURN study the estimation of the likely proportion of patients expected to have EGFR IHC-positive tumors based on study BR.21was shown to be higher than expected (but consistent with more recent Tarceva NSCLC studies, which have demonstrated greater rates of EGFR positivity staining than observed in BR.21), the other estimations used to predict sample size were confirmed by the results of the SATURN study.

3.1.3.2 Definition of Progression-free Survival

The primary efficacy parameter was duration of PFS (in the overall population and in patients with EGFR IHC-positive tumors), defined as the time from randomization to disease progression or death, whichever occurred first. Disease progression was defined according to the RECIST criteria. Both the investigator and a third-party independent central review determined response and date of disease progression. However, the assessment by investigators was defined by the study protocol to be the basis for the primary efficacy endpoint. Patients without an event (no disease progression or death) were censored at the date of their last tumor assessment where non-progression was documented. If a patient received a second anti-cancer therapy without prior documentation of disease progression, the patient was censored at the date of the last tumor assessment before starting the new anti-cancer therapy.

Objective progression (RECIST) was also the subject of a third-party independent central review of radiological images and any relevant clinical data, as prespecified in a central review charter. These datasets were used for corroboration of analysis of PFS and response. As described in the Charter for the Independent Central Reading of Image Data, which was approved by the FDA during the SPA process, 2 primary independent readers (radiologists) performed a blinded, centralized, independent assessment of image sets collected from patients who entered the randomized phase of the study. A complete set of images and any relevant clinical data from each patient, originating at the chemotherapy screening images and ending with the patient being off-study, was assigned to both independent readers. All pre-SATURN chemotherapy run-in period and SATURN study period images were evaluated by each reader. In the event of disagreement between the 2 primary readers, a third (adjudicator), who did not participate

in the primary reading, adjudicated. This adjudicator had to select 1 of the 2 previous response assessments in its entirety.

The analysis of PFS was to be performed after 731 events (patients with disease progression or death) had occurred. For patients without an event (no disease progression or death), a tumor assessment was required within the last 6 weeks before the clinical cut-off. For patients who had progressed, a survival assessment was required within the last 6 weeks before the clinical cut-off.

3.1.3.3 Definition of Overall Survival

Overall survival was defined as the time from randomization to date of death, irrespective of cause of death or subsequent therapy. Patients who had not died at the time of final analysis were censored at the date the patient was last known to be alive.

3.1.3.4 Determination of Response and Response Upgrade

To be randomized into SATURN, patients must have had a best response of either CR, PR, or SD during the chemotherapy run-in period. For patients to have a response during the randomized study period, a CR/PR/SD from the first-line chemotherapy must have been maintained or have improved. For patients with CR at randomization, a best response of continued CR required tumor-free follow-up measurements for at least 6 weeks postbaseline. For patients with PR or SD at randomization, a best response of CR or PR required follow-up measurements meeting the criteria for CR or PR at 2 consecutive visits at least 4 weeks apart at any time postbaseline. For best response, SD follow-up measurements had to meet the SD criteria for at least 6 weeks postbaseline.

A separate assessment of response upgrade was possible for patients with a PR or SD, if the best response improved at any 2 consecutive visits at least 4 weeks apart postbaseline.

3.1.4 Pharmacokinetic Evaluations

As a secondary objective, the pharmacokinetics of Tarceva in the target population was investigated, including the influence of covariates and post hoc estimates of exposure. Plasma samples were collected from all randomized patients in the SATURN study. All patients entering in the study were to have 5 pharmacokinetic (PK) samples taken as follows.

- Baseline visit (Day 1 of the study): 1 sample was taken before the first dose of study medication was administered
- Visit week 6: 1 predose sample, 1 postdose sample (time window between 3 – 5 hours)
- Visit week 12: 1 predose sample, 1 postdose sample (time window between 3 – 5 hours)

3.1.4.1 Other Secondary Endpoints

Quality of life as measured by the FACT-L was assessed by analyzing time to symptom progression and, although not specifically listed among the study's objectives, time to deterioration in trial outcome index and time to deterioration in quality of life. Exploratory post hoc quality of life analyses were also performed

Prospective and retrospective exploratory comparisons between additional molecular markers (ie, other than EGFR ICH) and clinical outcomes were also conducted.

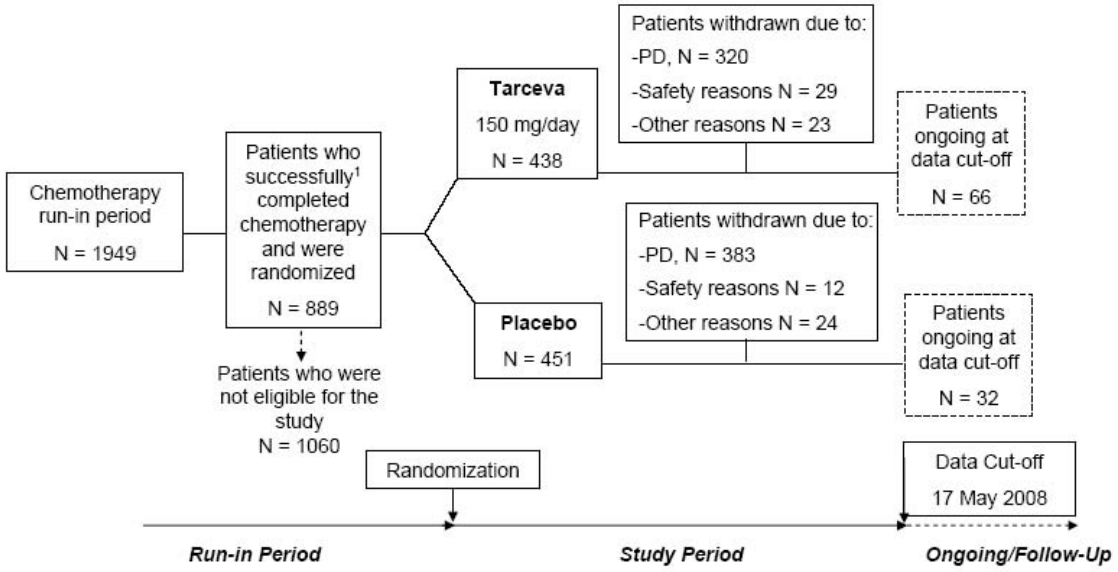
Although response rates (using RECIST criteria) and disease control were not specifically listed among the study's objectives, these analyses were also performed.

3.2 Results from SATURN Study

3.2.1 Patient Disposition

A total of 1949 patients entered the chemotherapy run-in period, as shown in **Figure 3-2**. Of these, 889 were randomized to receive either Tarceva 150 mg/day (438 patients) or placebo (451 patients) after having completed 4 cycles of platinum-based chemotherapy in the absence of unacceptable toxicity and/or PD. Reasons for not entering the study period following the chemotherapy run-in period included ineligibility (which included PD or failure to meet other eligibility criteria), patient refusal or decision not to enroll, or death. At the time of data cut-off for the primary end point analysis on 17 May 2008 (after 749 events of progression or death), 98 patients were still on study drug (66 on Tarceva and 32 on placebo). Following release of the study's primary endpoint results, patients were allowed to receive open-label Tarceva therapy based on the decision of the investigator and patient. The clinical cut-off for overall survival was 17 May 2009.

Figure 3-2: Schematic of Patient Disposition



[1]Patients were required to complete 4 cycles of platinum-based chemotherapy in the absence of unacceptable toxicity and/or PD to be eligible for study randomization

3.2.2 Patient Characteristics

Patient demographics and disease characteristics are summarized in **Table 3-1**.

The treatment groups were well balanced with respect to stratification factors, general demographic characteristics, smoking history, NSCLC characteristics (histology and stage), and tumor biomarker baseline status. The study population was predominantly male (74%) and Caucasian (83%) with approximately 15% of patients being of Asian origin. The median age of patients at randomization was approximately 60 years with an overall age range of 30 to 83 years. Most of the patients had metastatic NSCLC (Stage IV) at baseline (76% in placebo and 74% in Tarceva groups). Approximately two-thirds of all patients enrolled in this study had an ECOG PS of 1 and the remaining one-third had ECOG PS 0. The majority of patients were current smokers (55%, which includes patients who stopped smoking within a year prior to starting the study), with 18% being never smokers.

Adenocarcinoma and squamous cell carcinoma were the most frequent types of NSCLC (approximately 40% each). Other types of NSCLC represented altogether less than 15% of cases. Approximately half of randomized patients had responded to platinum-based chemotherapy (CR or PR) and the other half had stable disease at baseline.

Table 3-1: Key Demographics and Disease Characteristics at Randomization

Characteristic	Tarceva (N = 438)	Placebo (N = 451)
Age, median (range), years	60 (33 - 83)	60 (30 - 81)
Male / Female, %	73 / 27	75 / 25
Stage IIIB / IV, %	26 / 74	24 / 76
Caucasian / Asian / Other, %	84 / 14 / 1	83 / 15 / 1
ECOG PS: 0 / 1, %	31 / 69	32 / 68
Current / Former / Never smoker, %	55 / 28 / 18	56 / 27 / 17
Adenocarcinoma / Squamous / Other, %	47 / 38 / 15	44 / 43 / 13
EGFR IHC status: Positive / Negative / Indeterminate, %	70 / 14 / 16	69 / 13 / 18
Response to prior chemotherapy: CR / PR / SD / PD / Indeterminate, %	< 1 / 42 / 58 / < 1 / < 1	< 1 / 46 / 52 / < 1 / < 1
Prior radiotherapy: yes / no, %	11 / 89	10 / 90

Although the SATURN study was conducted outside of the United States, the demographic characteristics of the SATURN patient population discussed above are considered representative of the US patient population in this maintenance setting.

3.2.3 Tumor Sampling and Biomarker Status at Baseline

A summary of the tumor tissue sampling and biomarker status at baseline is provided in **Table 3-2**. Tumor biomarker analyses were performed in the following priority order: EGFR IHC, EGFR FISH, Kras mutations and EGFR mutations. Limitations in sample size and quality meant that successful analyses were not possible for all biomarkers from each sample.

The majority of patients had EGFR IHC-positive tumors (≥ 10% of tumor cells with any membranous EGFR staining, which is the definition used consistently throughout the Tarceva development program) with 69% in placebo and 70% in Tarceva group. Despite best efforts to determine the EGFR expression status for all patients, the status for this biomarker could not be determined for approximately 17% of patients due to poor quality of slides or insufficient tumor sample. Therefore 84% of patients with known EGFR IHC status had EGFR IHC-positive tumors. This EGFR IHC positivity rate is consistent with recent clinical studies conducted with Tarceva [7, 24, 27]. However, it was greater than observed in BR.21 and TRIBUTE (57% and 49%, respectively)[14].

There are multiple technical reasons that may underlie the different IHC results between SATURN and BR.21, including (1) pre-analytical factors, (2) different staining protocols,

(3) different scoring protocols, and (4) different pathologic interpretations. Although both the BR.21 and SATURN studies used the DAKO pharm DX kit using a ≥ 10% cut-off to define positivity, the IHC analyses were performed at different laboratories.

Because of differences in methodologies and potential reader differences between the testing laboratories, it is difficult to directly compare the results of these 2 studies. It can be speculated that the more rigorous standardization of pre-analytical factors in SATURN may have resulted in less epitope degradation and thus a greater EGFR positivity rate. The similarity of the SATURN results to those reported in other, more recent studies, suggests the EGFR ICH-positivity rates observed in SATURN may be a more accurate reflection of IHC positivity in the advanced NSCLC setting than those observed in the BR.21 study.

For EGFR FISH, EGFR mutation status, and Kras mutation status, the treatment groups were generally well balanced, as shown in **Table 3-2**. The frequencies (incidences) for the biomarkers are consistent with the known incidences of these biomarkers in advanced NSCLC.

Table 3-2: Summary of Biomarker Status at Baseline

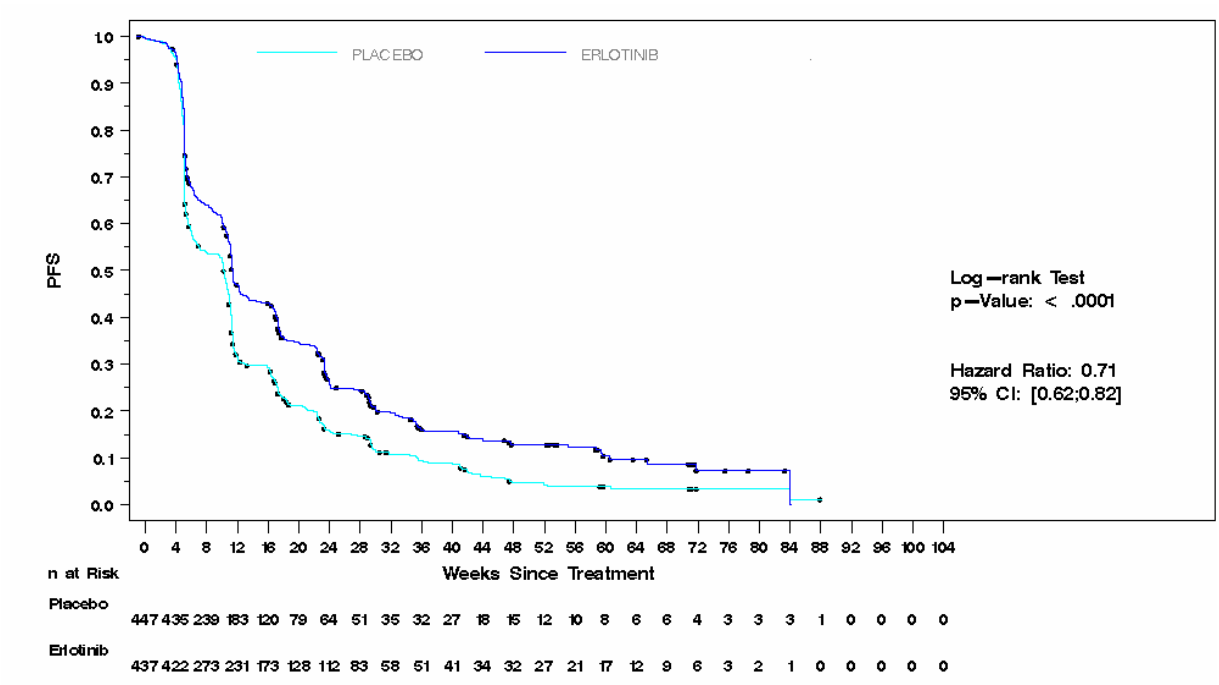
	TARCEVA (N=438) N (%)	PLACEBO (N=451) N (%)
Tumor Site		
Metastasis	107 (24%)	104 (23%)
Primary Tumor	331 (76%)	346 (77%)
N	438	450
Sample Preparation		
Block	303 (69%)	283 (63%)
Slide(S)	135 (31%)	167 (37%)
N	438	450
EGFR IHC		
Positive	308 (70%)	313 (69%)
Negative	62 (14%)	59 (13%)
Indeterminate	16 (4%)	24 (5%)
Missing	52 (12%)	55 (12%)
N	438	451
EGFR FISH		
Positive	121 (28%)	111 (25%)
Negative	128 (29%)	128 (28%)
Indeterminate	51 (12%)	64 (14%)
Missing	138 (32%)	148 (33%)
N	438	451
EGFR Mutation Status		
Activating Mutation	22 (5%)	27 (6%)
Resistance Mutation	1 (< 1%)	(0%)
Other Mutation	6 (1%)	2 (< 1%)
Wild Type	199 (45%)	189 (42%)
Indeterminate	33 (8%)	39 (9%)
Missing	177 (40%)	194 (43%)
N	438	451
Kras Mutation Status		
Classic Mutation	49 (11%)	41 (9%)
Other Mutation	(0%)	1 (< 1%)
Wild Type	205 (47%)	198 (44%)
Indeterminate	26 (6%)	30 (7%)
Missing	158 (36%)	181 (40%)
N	438	451

3.2.4 Progression-free Survival

3.2.4.1 Co-Primary endpoints

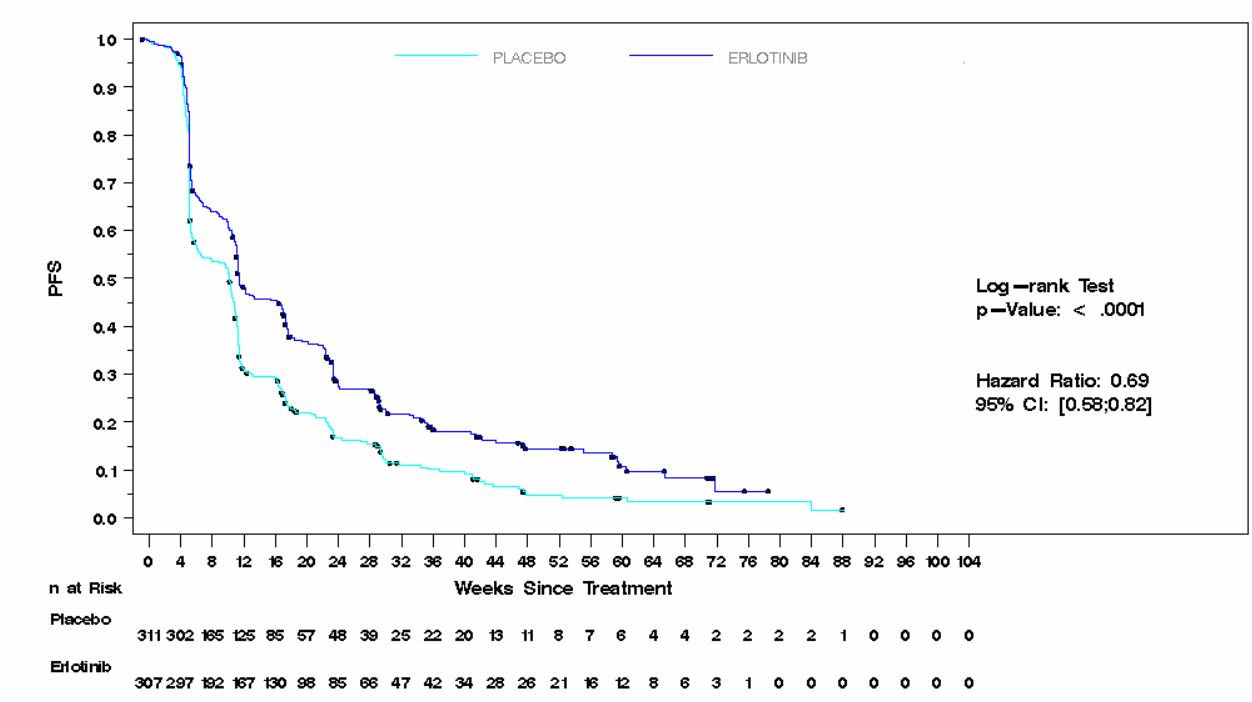
SATURN met its co-primary endpoints by demonstrating a highly statistically significant improvement in investigator-assessed PFS in the overall population (HR = 0.71; $P < 0.0001$) as well as for patients with EGFR IHC-positive tumors (HR = 0.69; $P < 0.0001$), as shown in **Figure 3-3** and **Figure 3-4**. This corresponded to PFS improvements of 41% and 45% in the overall population and EGFR IHC-positive population respectively. Median PFS was 11.1 weeks (95% CI 8.1 to 11.7) in the placebo group versus 12.3 weeks (95% CI 12.0 to 13.3) in the Tarceva group. The 6-month estimate of PFS rate was 25% in the Tarceva group compared with 15% in the placebo group. However, due to the "stair-step" shape of the Kaplan-Meier curves (most notably, the "pinching" of the curves around the time of the medians), the median estimates do not capture the true clinical benefit of treatment with Tarceva over the entire study duration as well as the hazard ratios of 0.71 and 0.69 for the overall population and EGFR IHC-positive population, respectively ($P < 0.001$ in both). Indeed, once the KM curves separate, they remain separated for the duration of the treatment period. Given the high proportion of patients with an event, calculation of means was considered valid: mean PFS was 16.0 weeks in the placebo group compared with 22.4 weeks in the Tarceva group.

Figure 3-3: Kaplan-Meier Curve of Progression-free Survival (Full Analysis Set)



Note: number of patients in PFS analysis is less than total FAS because of exclusion of patients who had PD before randomization.

Figure 3-4: Kaplan-Meier Curve of Progression-free Survival (EGFR IHC-Positive Analysis Set)



3.2.4.2 Central Radiology Review Assessment of Progression-free Survival

As shown in **Table 3-3**, the results of the assessment conducted by the central radiology review were close to identical to the assessment of PFS conducted by the investigators for all patients (HR = 0.71, 95% CI 0.61 to 0.84, $P < 0.0001$). There was also strong concordance between the investigators and the central radiology review in the EGFR IHC-positive population.

Table 3-3: Concordance Between Investigator and Independent Reviewers

	Tarceva (N = 438)	**Placebo (N = 451)**	***P* value HR/CI**
Independent Reviewer			
Time to event (weeks) Median (95% CI)	12.3 (12.0 – 15.0)	11.1 (7.7 – 11.9)	$P = < 0.0001$ HR 0.71 (0.61 – 0.84)
Investigator			
Time to event (weeks) Median (95% CI)	12.3 (12.0 – 13.3)	11.1 (8.1 – 11.7)	$P = < 0.0001$ HR 0.71 (0.62 – 0.82)

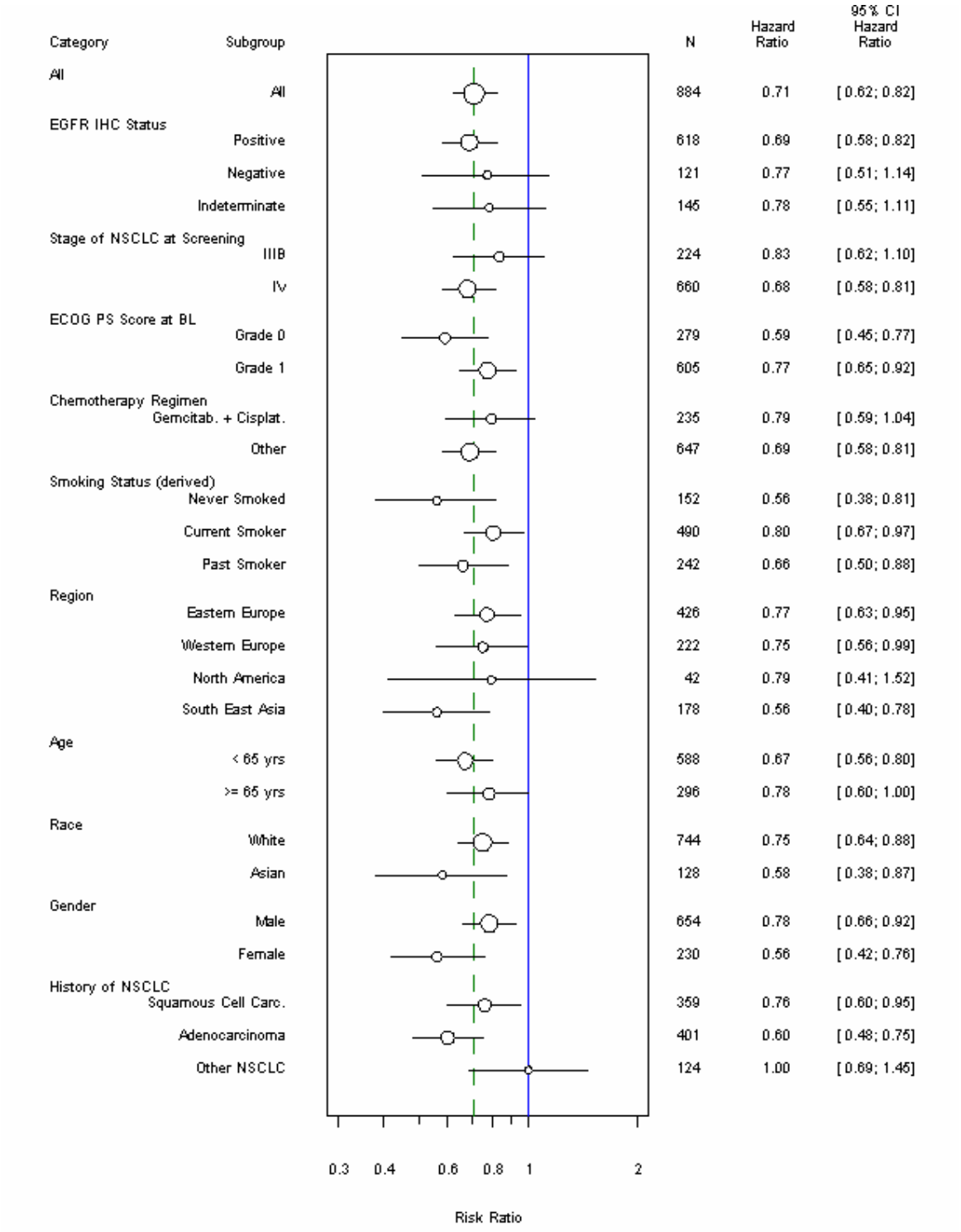
There was some discrepancy between investigators and the central radiology review regarding the timing of progression. The timing concordance rate was 82% for the placebo group and 78% for the Tarceva group, with approximately two-thirds of discordances in timing being less than 1 week.

The process for resolving discrepancy was predefined in the charter for the central radiology review assessment, and is described in **Section 3.1.3.2**.

3.2.4.3 Subgroup Analyses

Results from exploratory subgroup analyses were consistent with the PFS benefit seen in the overall patient population (see **Figure 3-5**). Efficacy was observed across major histological types, smoking status, gender, race, ECOG PS, and other clinical characteristics. In particular, patients with adenocarcinoma as well as patients with squamous cell carcinoma derived statistically significant benefit from treatment with Tarceva. Patients with squamous histology had a HR of 0.76, while patients with adenocarcinoma had a HR of 0.60.

Figure 3-5: Forest Plot of Hazard Ratios and 95% Confidence Intervals for PFS by Subgroup (Stratification Factors, Demographic, and Baseline Characteristics) Full Analysis Set (FAS)



3.2.4.4 Effect of EGFR Protein Expression Status on PFS

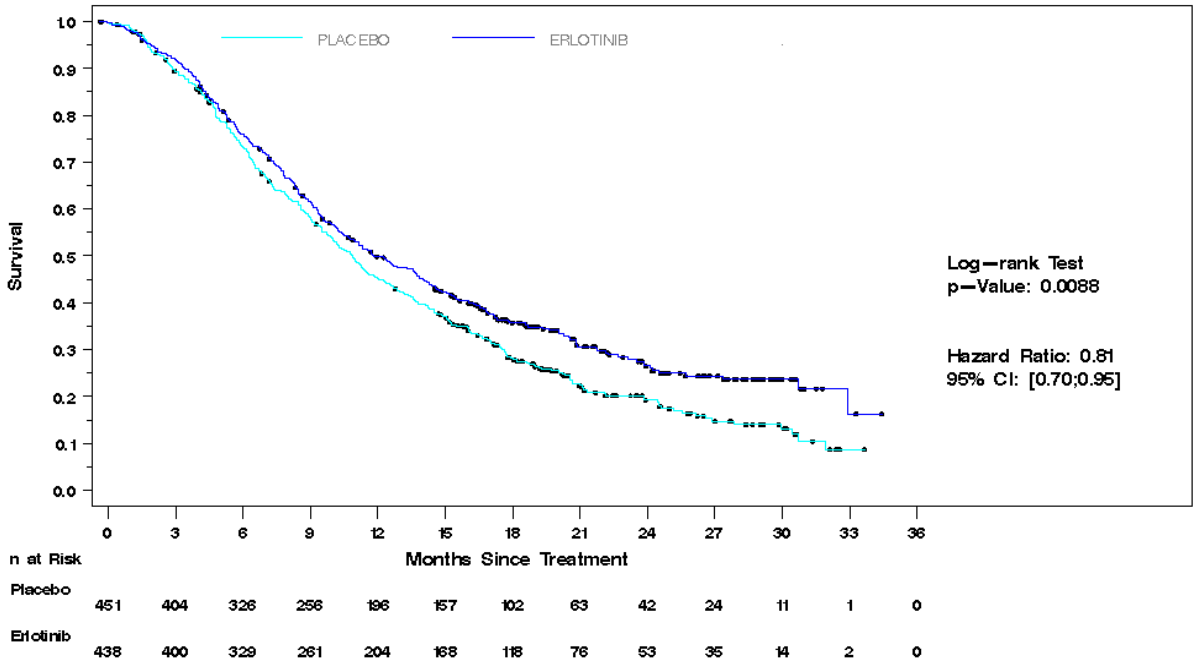
As described in **Section 3.2.4.1**, a co-primary endpoint of the SATURN study was the difference in PFS in the EGFR IHC-positive population. The magnitude of benefit in PFS derived by the EGFR IHC-positive population was similar to that observed for the overall population: HR = 0.69 versus HR = 0.71, respectively (see **Figure 3-4**). Evaluation of the IHC-negative subgroup was a secondary endpoint. Only 16% of patients with known IHC status were IHC-negative (n = 121). As shown in **Figure 3-5**, a benefit was seen in the IHC-negative subgroup (HR = 0.77, *P* = 0.1768). The lack of statistical significance is likely due to the small number of patients in this subgroup (62 in the Tarceva group and 59 in the placebo group). There was no evidence of a differential effect on PFS based on IHC status; the interaction test between IHC status and treatment was not statistically significant (*P* = 0.6312). EGFR IHC status was therefore not considered to be a useful discriminator for clinical benefit in this study.

3.2.5 Secondary Endpoints

3.2.5.1 Overall Survival

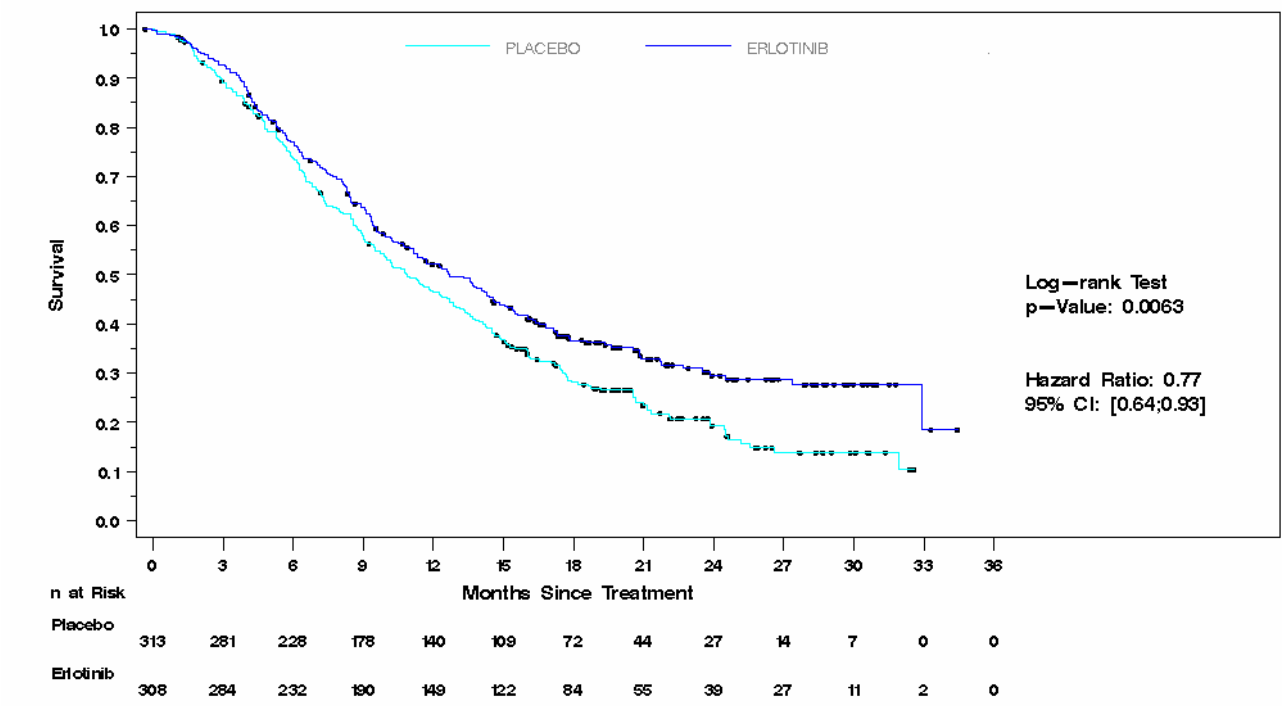
In the overall population, benefit in PFS translated into a statistically significant and clinically relevant benefit in OS: HR = 0.81 (95% CI: 0.70;0.95, *P* value = 0.0088). The median OS was 11.1 versus 12.8 months, and 1-year survival was 45% versus 50% in the placebo and Tarceva arms, respectively. The OS curves separate early and continue to separate after the median point (see **Figure 3-6**).

Figure 3-6: Kaplan-Meier Curve of Overall Survival in Overall Population



Similar to OS results in the overall population, there was clinically relevant benefit in OS for the EGFR IHC-positive population (see **Figure 3-7**): HR = 0.77 (95% CI: 0.64; 0.93, *P* value = 0.0063). Median OS was 11.0 versus 12.8 months in the placebo and Tarceva arms, respectively. The one-year survival was 45% versus 50% in the placebo and Tarceva arms respectively. Although the difference in OS did not reach statistical significance in the EGFR IHC-negative population (HR = 0.91, *P* = 0.6482), benefit from Tarceva for patients with IHC-negative tumors cannot be ruled out.

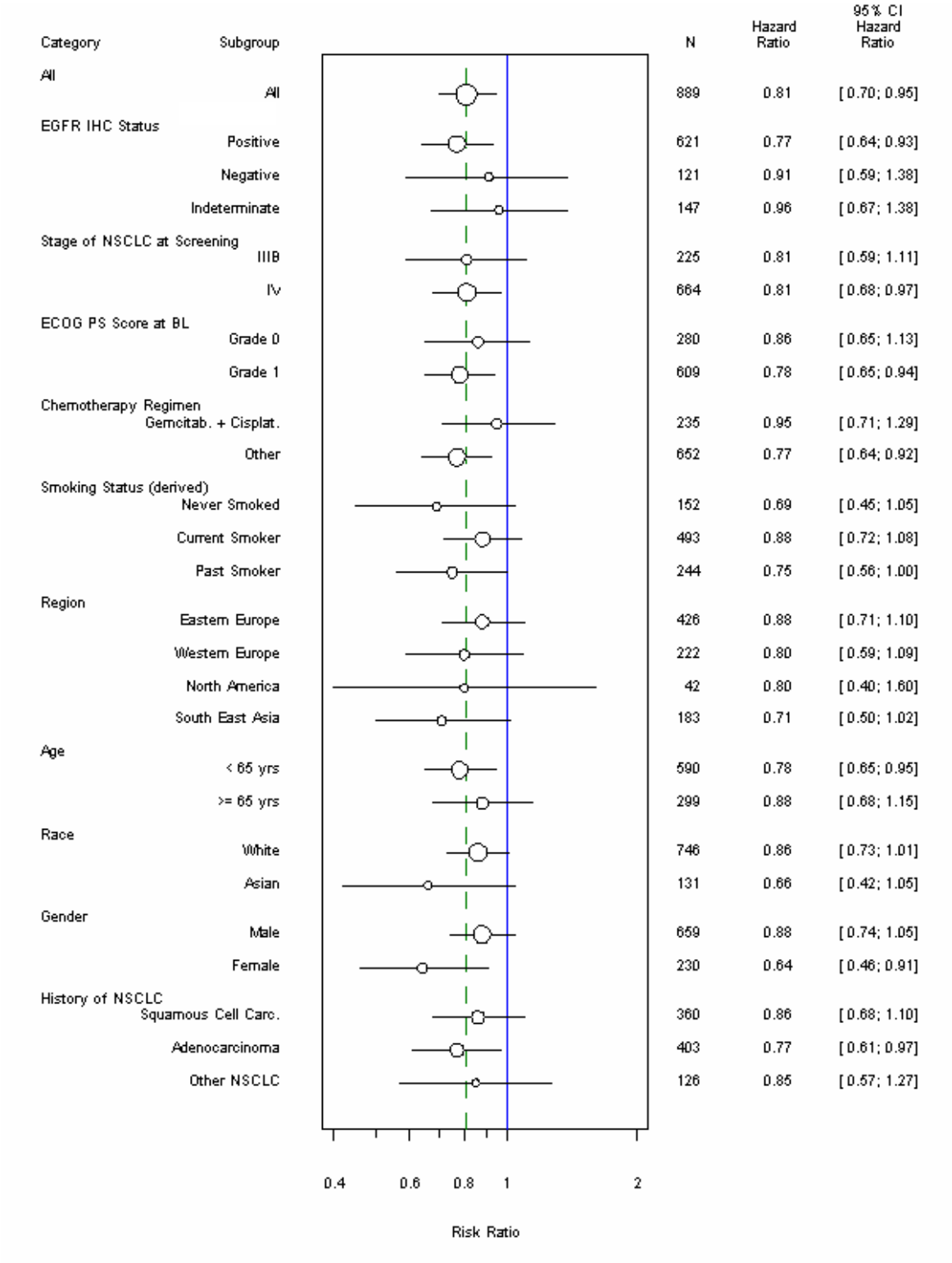
Figure 3-7: KM Curve of Overall Survival in EGFR IHC-Positive Population



3.2.5.2 Overall Survival Subgroup Analysis

As was observed with PFS, subgroup analyses showed robust and consistent OS benefit from Tarceva across subgroups (**Figure 3-8**). All HR estimates were below 1.00, suggesting that patients benefited or likely benefited from Tarceva treatment irrespective of their demographic characteristics, ECOG PS status at baseline, previous treatment, and histology of NSCLC. Patients with adenocarcinoma (HR = 0.77) and patients with squamous cell carcinoma (HR = 0.86) benefited from Tarceva treatment (**Figure 3-8**). Similar OS results were observed in the EGFR IHC-positive population (HR = 0.77).

Figure 3-8: Forest Plot of Hazard Ratios and 95% Confidence Intervals for Overall Survival by Subgroup (Stratification Factors, Demographics, and Baseline Characteristics) Full Analysis Set (FAS)



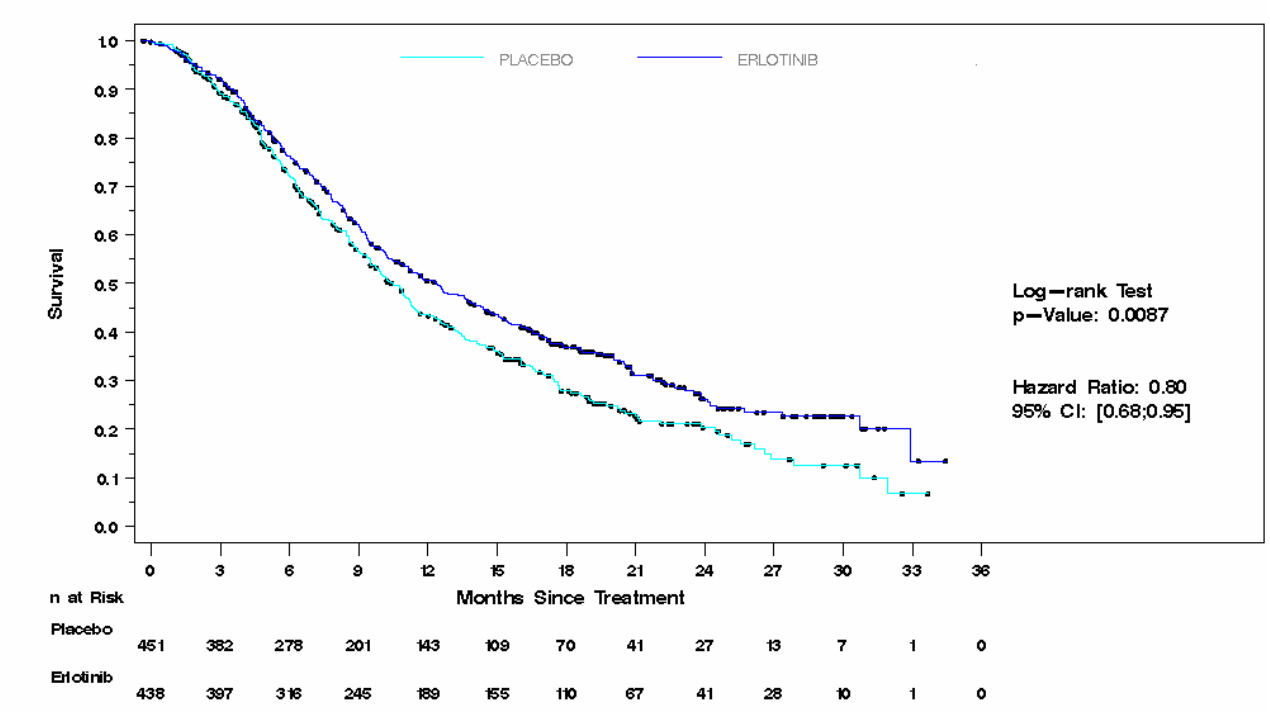
3.2.5.3 Overall Survival and Further-line Therapy

In a first-line study, OS results can be confounded by use of subsequent therapies, since many patients will go on to receive proven efficacious therapy in the second-line after disease progression. In the SATURN study, a high proportion of patients took second-line or further therapy. In the placebo arm 66% received second or further lines of therapy (including chemotherapy single agent, doublets, or TKIs), while in the Tarceva arm 63% received further therapy. Among the poststudy systemic treatments, more patients in the placebo group received TKIs, including EGFR inhibitors, than in the Tarceva group (21% compared with 11%, respectively).

In all settings, second-line, third-line, and further, single agent or combination agent, numerically fewer patients on the Tarceva arm received subsequent therapies compared with patients on the placebo arm. Given that second-line therapy in advanced NSCLC is known to improve survival, the higher number of patients receiving subsequent therapy on the placebo arm would suggest that additional therapy does not explain the statistically significant improvement in OS with Tarceva. The relatively large number of placebo patients who may not receive additional therapy also highlights the value of treatment with Tarceva in the maintenance setting.

Investigators in the SATURN trial could request unblinding of patients at progression to enable use of open-label Tarceva. Therefore, a post-hoc analysis of OS censored by first open-label Tarceva or second and further-line tyrosine kinase inhibitors (TKIs) was conducted (see **Figure 3-9**). The benefit in OS in the overall population remained statistically significant ($P = 0.0087$) with a similar magnitude of benefit as the main OS analysis (HR = 0.80). However, there was a larger absolute difference in medians, 10.6 and 12.5 months in placebo and Tarceva arms, respectively.

Figure 3-9: Kaplan-Meier Curve of Overall Survival Censored by First Open Label Tarceva or Second and Further-line Tyrosine Kinase Inhibitors



3.2.5.4 PFS and OS in Exploratory Biomarker Subgroups

In the SATURN study, exploratory analyses of PFS and OS among the biomarker subgroups indicated that Tarceva treatment should be considered as an option across all biomarker subgroups, as all groups have an HR below 1.0, demonstrating that they all derive benefit. Forest plots of hazard ratio for PFS and OS by biomarker status are shown in **Figure 3-10** and **Figure 3-11**.

Previous studies have indicated that tumors with EGFR activating mutations (exon 19 and L858R) have dramatic responses to EGFR TKI inhibitors [28, 35]. In SATURN, activating EGFR mutations identified patients with greatest PFS benefit (HR = 0.10, $P < 0.0001$), although patients with EGFR wild type tumors also benefited (HR = 0.78, $P = 0.0185$), demonstrating that, while EGFR mutations confer exceptional benefit, they are not a prerequisite for benefit from treatment with Tarceva. Overall survival data in the EGFR mutation positive subgroup are still immature as only 8 of the 22 Tarceva-treated EGFR mutation positive patients have died and the analyses are confounded by the fact that 67% of patients with EGFR mutation positive tumors in the placebo arm received a second-line EGFR TKI.

Some small retrospective studies have concluded that NSCLC patients with Kras mutations might not derive benefit from treatment with tyrosine kinase inhibitor (TKIs) while other studies have not supported this conclusion [34, 36]. In SATURN, the HR for PFS and OS in the Kras mutation positive subgroup (codons 12 or 13 in exon 2 or codon 61 in exon 3) was 0.77 ($P = 0.2246$) and 0.79 ($P = 0.3254$), respectively, compared with a PFS HR of 0.70 and OS HR of 0.86 in the wild-type Kras subgroups, indicating that both groups derived benefit from treatment with Tarceva (see **Figure 3-10**).

Study BR.21 indicted that patients whose tumors had an increase in EGFR copy numbers, as determined by EGFR FISH, derived greater benefit from Tarceva [35, 37, 38]. More recent studies have provided mixed results regarding the predictive capability of EGFR FISH for EGFR-TK inhibitors [13, 24, 39]. In SATURN, patients derived benefit in PFS regardless of EGFR FISH status: HR = 0.68 in the EGFR FISH positive subgroup versus 0.81 in the EGFR FISH negative subgroup versus 0.71 in the overall population (see **Figure 3-10**).

Figure 3-10: Forest Plot of Hazard Ratios and 95% Confidence Intervals for PFS by Biomarker Status

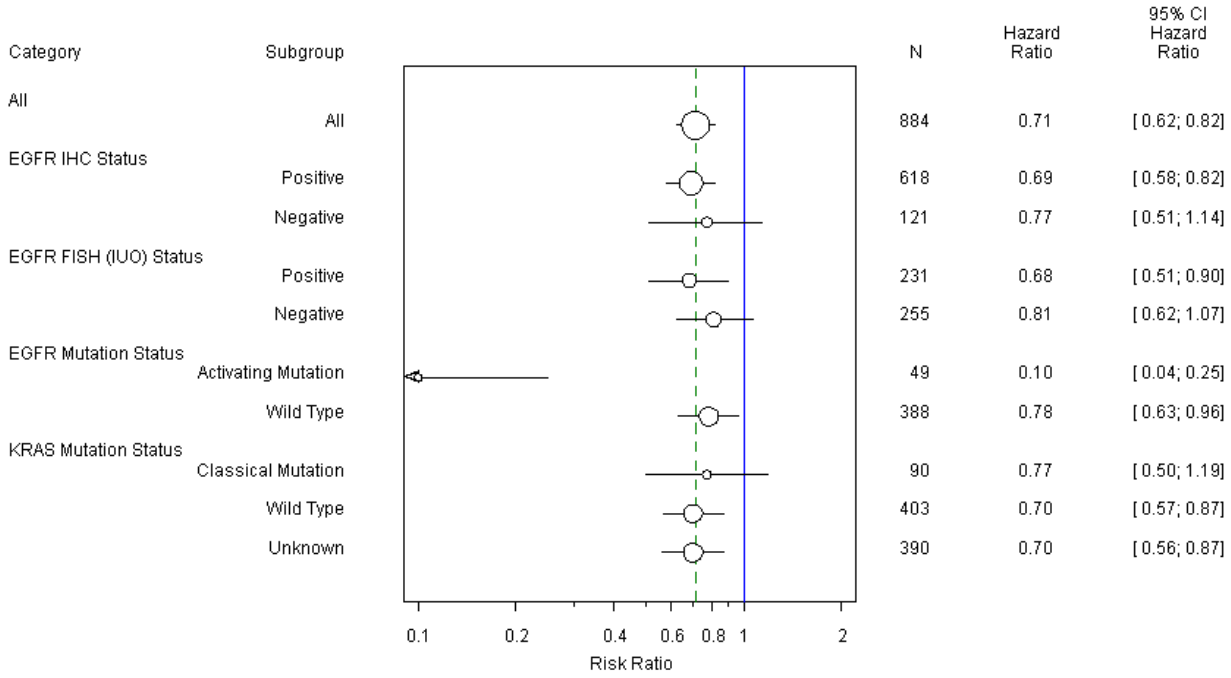
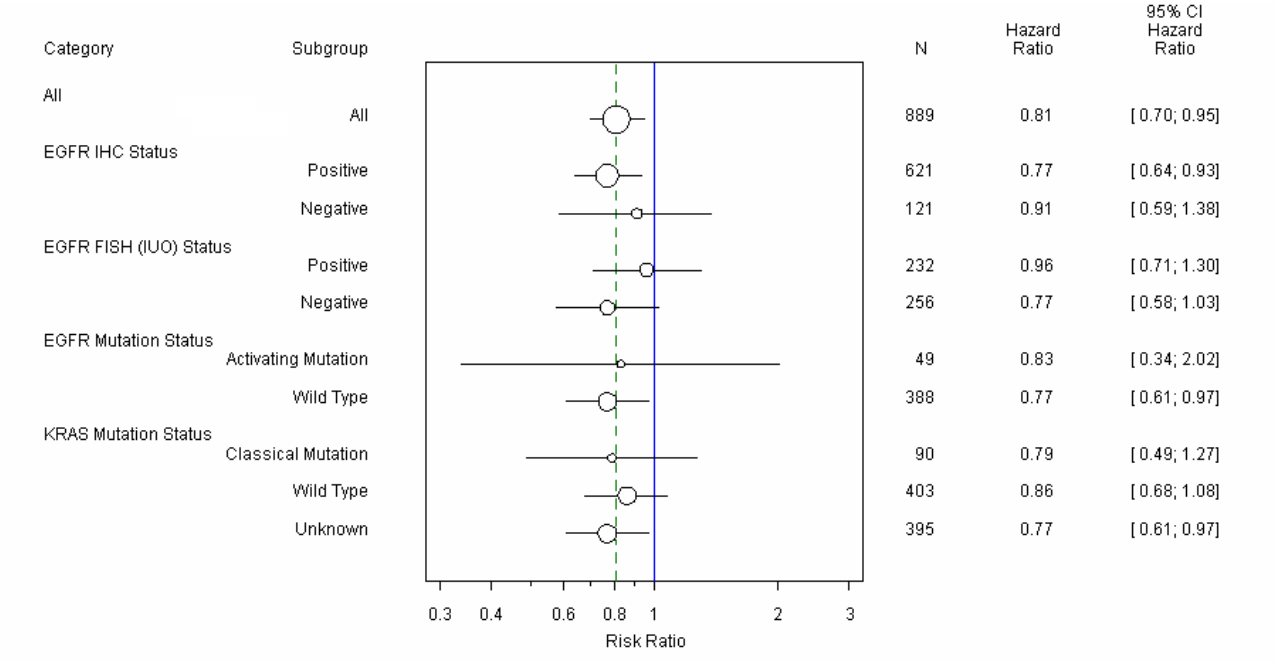


Figure 3-11: Forest Plot of Hazard Ratios and 95% Confidence Intervals for OS by Biomarker Status



3.2.5.5 Robustness Analyses for PFS and OS

Several sensitivity analyses were performed to assess the robustness of the PFS and OS results. The robustness of the PFS assessment by the investigator was corroborated by the results of the independent central review of radiological and clinical data, as described in **Section 3.2.4.2**.

Cox regression models, adjusting for the stratification factors and using a stratified analysis, were conducted for PFS and OS using the stratification factors from randomization (ECOG PS, EGFR IHC, stage of NSCLC at screening, chemotherapy regimen, smoking status, and region). Results in the overall population were similar to the primary, unstratified analyses in both the adjusted model (PFS: HR = 0.72, $P < 0.0001$; OS: HR = 0.82, $P = 0.01$) and the stratified analysis (PFS: HR = 0.70, $P < 0.0001$; OS: HR = 0.85, $P = 0.08$).

The robustness of the PFS and OS analyses were also confirmed by consistent results across multiple subgroups (see **Figure 3-5**). Efficacy was observed irrespective of histology, smoking status, gender, race, ECOG PS or other clinical characteristics. Benefit was also seen across all biomarker subgroups. Of note, benefit was seen in EGFR wild-type patients as well as patients with an activating EGFR mutation.

Preplanned analyses of PFS included sensitivity analyses to account for the potential impact of missing or inevaluable disease assessments. In one case, the patient's PFS was censored at the first missing assessment visit (PFS HR = 0.71, $P < 0.0001$). In another analysis, the patient was considered to have progressed at the first missing assessment visit (PFS HR = 0.71, $P < 0.0001$).

Another preplanned sensitivity analyses for PFS was performed for the Per Protocol population. The Per Protocol population (N = 853) consisted of patients who received study drug, had at least 1 postbaseline assessment or died prior to first postbaseline assessment, and who did not have a major protocol violation. The HR for PFS was 0.69 ($P < 0.0001$).

3.2.5.6 Response Rate

Patients in the Tarceva arm achieved a significantly higher response rate compared with the placebo arm (11.9% versus 5.4% respectively, $P = 0.0006$) and response upgrade rate (5.5% versus 1.3% respectively, $P = 0.0007$). As shown in **Table 3-4**, the disease control rate (ie, CR+PR+SD) was also higher in the Tarceva group compared with the placebo group (60.6% versus 50.8% respectively, $P = 0.0035$) as well as the disease control with SD lasting more than 12 weeks (SD for more than 12 weeks plus PR or CR, 40.8% versus 27.4% respectively, $P < 0.0001$). Thus, treatment with Tarceva in the maintenance setting allows not only the consolidation of response to chemotherapy, but also builds further on the effects of chemotherapy.

Table 3-4: Summary of Response and Disease Control Rate – All patients

	TARCEVA (N=436)		PLACEBO (N=445)
CR + PR + SD	264 (60.6%)		226 (50.8%)
95% CI for CR+PR+SD Rates	[55.8; 65.2]		[46.0; 55.5]
Difference in Disease Control Rates		9.8	
95% CI for Difference in Disease Control Rates		[3.1; 16.4]	
P value (Chi-squared Test)		0.0035	
CR + PR + SD>12 Weeks	178 (40.8%)		122 (27.4%)
95% CI for CR+PR+SD>12 Weeks Rates	[36.2; 45.6]		[23.3; 31.8]
Difference in Disease Control Rates		13.4	
95% CI for Difference in Disease Control Rates		[7.1; 19.7]	
P value (Chi-squared Test)		< .0001	

3.2.5.7 Time to Symptom Progression and Other Patient-Reported Quality of Life Analyses

Although time to symptom progression was the only stated patient-reported quality of life (QoL) study objective, other predefined QoL analyses were performed: time to deterioration in trial outcome index (measures physical functioning of the patients) and time to deterioration in QoL. Several post hoc QoL analyses were also performed, which included time to pain, analgesics use, cough, and dyspnea. QoL was assessed using the Functional Assessment of Chronic Illness Therapy - Lung (FACT-L) QoL instrument. FACT-L completion rates were above 90% at almost all study visits and were similar in both treatment groups. However, because the patients stopped completing the questionnaire after PD, and Tarceva increased PFS, the absolute number of patients who completed the questionnaire decreased more rapidly in the placebo group when compared with the Tarceva group.

The time to symptom progression was similar in both treatment groups (HR = 0.91, $P = 0.3787$) as was time to deterioration in trial outcome index (HR = 1.06, $P = 0.5385$), and time to deterioration in quality of life (HR = 0.96, $P = 0.6530$). Given that patients were evaluated frequently (every 6 weeks) with radiological imaging, radiological progression may have been detected sooner than patients manifested symptom

progression, thus limiting the ability to detect differences in this assessment scale. In the maintenance setting after first-line chemotherapy, where tolerability of therapy and preservation of quality of life is important, it is notable that no deterioration in quality of life was seen among patients receiving Tarceva when compared with patients receiving placebo.

Patients appeared to derive palliative benefit from treatment with Tarceva in this disease setting as illustrated by post hoc analyses of the time to pain and the time to analgesics (opioid and other analgesics), which were significantly longer for patients receiving Tarceva (HR 0.61, $P = 0.008$ and HR 0.66, $P = 0.0199$, respectively). Other parameters investigated, time to cough (HR = 0.77) and time to dyspnea (HR = 0.75), also indicated benefit from Tarceva, although these results were not statically significant ($P = 0.2546$ and 0.2054, respectively).

3.2.5.8 Pharmacokinetics Results

A total of 308 patients in the SATURN study were eligible for pharmacokinetic (PK) analysis. These patients were treated with Tarceva and had at least 1 measurable plasma concentration postdose. A total of 882 plasma samples with measurable erlotinib concentrations were collected from 308 patients. Of these patients, 15 had measurable plasma concentrations at the baseline visit (before any drug intake), and 2 patients had implausible high plasma concentrations without any or long after any documented drug intake. These unexpected values were considered to be due to normal sampling or data recording errors. Therefore, these 17 patients were excluded from the analysis. Data from 291 patients were available for the PK analysis.

The population pharmacokinetic data obtained in SATURN were in line with those reported previously in patients with Stage IIIB/IV NSCLC (see Package Insert, **Section 6.1**). Consistent with previous population PK analyses, apparent clearance was slightly higher in current smokers (by ≈ 20%) compared with those who never smoked. No obvious relationship between measures of exposure and either efficacy or safety parameters could be identified.

3.3 Efficacy Conclusions

While first-line platinum-based chemotherapy has improved survival and quality of life for patients with advanced NSCLC, this therapy is not curative and many patients rapidly

progress despite initial benefit, and the majority will die within a year of diagnosis. Thus, a large medical need remains in this patient population.

SATURN demonstrated a clinically meaningful and statistically significant improvement in PFS and OS for all patients as well as for patients with EGFR IHC-positive tumors. Efficacy was shown across study subgroups irrespective of histology, race, gender, smoking status, and ECOG PS.

In the SATURN study, exploratory analyses of PFS and OS among the biomarker subgroups indicated that Tarceva treatment should be considered as an option across all biomarker subgroups. All groups had an HR below 1.0, demonstrating that they all derive benefit. Although the greatest benefit was observed in the subgroup of patients with EGFR activating mutation, significant benefit was also observed in the EGFR wildtype subgroup.

Tarceva is an oral drug that has shown efficacy in patients with Stage IIIB/IV not only in adenocarcinoma but also in squamous-cell carcinoma in a first-line maintenance placebo-controlled study, and can therefore respond to an unmet medical need in this difficult-to-treat patient population. It is easily administered due to its oral formulation and requires no out-patient infusion center or hospital-stay. Treatment with Tarceva demonstrated no deterioration in quality of life when compared with patients who were receiving best supportive care (ie, the placebo group).

3.4 Safety of Single-Agent Tarceva in First-Line NSCLC Maintenance

3.4.1 Summary of Safety Results from SATURN Study

3.4.1.1 Exposure

In the SATURN study, 433 patients were exposed to at least 1 dose of Tarceva (150 mg/day) and 445 patients to placebo. Eleven patients were excluded from the safety population (6 placebo and 5 Tarceva) either because they did not receive at least 1 dose of study drug or because they inadvertently were dispensed both study drugs (Tarceva and placebo, 3 patients in each treatment arm). The median total cumulative dose of Tarceva was 12,750 mg with median exposure duration of 12.3 weeks. As expected due to the shorter PFS, the placebo group had shorter median duration of exposure (11.7

weeks). Ninety-five patients (22%) received study drug for more than 6 months in the Tarceva group compared with 58 patients (13%) in the placebo group.

Overall, the proportion of patients needing dose reductions or interruptions was low. Although the majority of patients in the Tarceva group maintained the initial starting dose of 150 mg daily throughout the study (the median dose intensity was 150 mg), 47 patients (11%) had their Tarceva dose reduced to 100 mg daily and 4 patients had a reduction to less than 100 mg daily. In the placebo group, 3 patients (< 1%) had dose reductions. Forty-one patients (10%) in the Tarceva group had a dose interruption of less than 1 week (placebo group 21 patients, 5%), while 26 patients (6%) in the Tarceva group had dose interruptions lasting 1 week or more (placebo 6 patients, 1%).

3.4.1.2 Overview of Adverse Events

Although most patients in the Tarceva group experienced at least 1 AE, only 4.6% (20 patients) permanently discontinued taking study drug due to an AE regardless of causality (placebo group 7 patients, 1.6%) and 16.2% had a dose modification or interruption due to an AE (placebo group 3.4%). In the Tarceva group, the most common AEs considered related to the study drug by the investigators were rash (48.5%) and diarrhea (18.2%). Only 12 patients (2.8%) withdrew from the study in the Tarceva group due to AEs considered by the investigator to be related to the study drug. Sixty-six patients died during the treatment phase, 35 patients in the Tarceva group (8.1%) and 31 patients in the placebo group (7.0%). Most were due to progressive disease (6% of deaths in each group), while 10 patients in the Tarceva group and 5 patients in the placebo group experienced grade 5 (fatal) AEs. One was considered drug-related (interstitial lung disease [ILD] with final cause of death considered by the Investigator to be progressive disease) occurring in a Tarceva-treated patient.

3.4.1.3 Common Adverse Events

Consistent with findings from other clinical studies of single-agent Tarceva, rash (49.2%) and diarrhea (20.3%) are the most commonly reported adverse events in the Tarceva group. These were the only adverse events with an incidence ≥ 10%.

Adverse events regardless of causality that occurred with an incidence ≥ 3% among Tarceva-treated patients are listed in **Table 3-5**. Adverse events for which the incidence in the Tarceva arm was notably higher than in the placebo arm include several skin and subcutaneous tissue disorders (rash [49.2% vs 5.8%], pruritus [7.4% vs 2.7%], acne [6.2% vs 0%], dermatitis acneiform [4.6% vs 1.1%], and dry skin [4.4% vs < 1%]), as well as diarrhea (20.3% vs 4.5%), nausea (7.6% vs 6.1%), fatigue (9.0% vs 5.8%), asthenia (4.2% vs 2.9%), pneumonia (3% vs 1.6%), paronychia (3.9% vs 0%), anorexia (9.2% vs 4.9%), and weight decrease (3.9% vs < 1%).

Table 3-5: Adverse Events With an Incidence ≥ 3% Higher in Tarceva Group than Placebo Group (Safety Population)

Adverse Event	Tarceva N=433						Placebo N=445					
	All		G3		G4		All		G3		G4	
	n	%	n	%	n	%	n	%	n	%	n	%
Rash	213	49.2	26	6.0	-	-	26	5.8	-	-	-	-
Diarrhoea	88	20.3	8	1.8	-	-	20	4.5	-	-	-	-
Fatigue	39	9.0	8	1.8	-	-	26	5.8	5	1.1	-	-
Anorexia	40	9.2	2	<1	-	-	22	4.9	1	<1	-	-
Pruritus	32	7.4	1	<1	-	-	12	2.7	-	-	-	-
Acne	27	6.2	3	<1	-	-	-	-	-	-	-	-
Dermatitis Acneiform	20	4.6	4	<1	-	-	5	1.1	-	-	-	-
Dry Skin	19	4.4	-	-	-	-	4	<1	-	-	-	-
Weight Decreased	17	3.9	1	<1	-	-	4	<1	-	-	-	-
Paronychia	17	3.9	3	<1	-	-	-	-	-	-	-	-

3.4.1.4 Severity of Adverse Events

The majority of AEs were NCI-CTCAE grade 1 or grade 2 (75.3% of patients in the Tarceva group and 87.9% in the placebo group experienced no ≥ grade 3 event). Twice as many patients in the Tarceva group experienced ≥ grade 3 AEs compared with the placebo group (107 patients, 24.7%, vs 54 patients, 12.1%), which includes 26 patients (6.0%) in the Tarceva group who experienced severe (all grade 3) rash, compared with none in the placebo group, and 8 patients (1.8%) who experienced severe (all grade 3) diarrhea, compared with none in the placebo group.

Among the patients with ≥ grade 3 AEs, 58 patients (6.6%) experienced events considered by the investigator to be related to study drug (4 in the placebo group, 0.9%, and 54 in the Tarceva group,12.5%). Of the 54 related severe adverse events in the Tarceva group, rash was the most frequent (26 patients, 6.0%), followed by diarrhea (7 patients, 1.6%), dermatitis acneiform (4 patients, 0.9%), acne (3 patients, 0.7%), paronychia (3 patients, 0.7%), fatigue (2 patients, 0.5%), and rash generalized (2 patients, 0.5%). All others were single events.

Four patients in the Tarceva group had a grade 4 AE (gastric perforation, dyspnea, myalgia, and intracranial pressure increased) compared with 6 patients in the placebo group (hemoptysis, muscular weakness, peripheral ischemia, anemia, myocardial infarction, and hepatic pain).

3.4.1.5 Investigator Assessed Relationship to Study Treatment

Approximately two-thirds of the patients in the Tarceva arm (281 patients, 64.9%) compared with one-fifth of the patients in the placebo group (89 patients, 20.0%) experienced AEs considered by the investigator to be related to study treatment. In the Tarceva group, the most common AEs regarded as related were rash (210 patients, 48.5%; placebo 4.9%) and diarrhea (79 patients, 18.2%; placebo 3.1%). In the Tarceva group, 8.3% and 3.2% of patients had dose interruptions or reductions due to rash and diarrhea, respectively, and only 5 patients and 2 patients discontinued study drug due to these related events.

Other AEs in the Tarceva group regarded as related in at least 3% of patients included pruritus (6.2%, placebo 2.0%), acne (6.2%, placebo 0%), dermatitis acneiform, (4.6%; placebo 1.1%) anorexia (5.1%, placebo 2.2%), nausea (4.2%, placebo 3.4%), dry skin (4.2%, placebo 0.9%), fatigue (3.9%, placebo 2.2%), and paronychia (3.5%, placebo 0%).

3.4.1.6 Adverse Events of Special Interest

Before unblinding of the study, and in light of the known safety profile of Tarceva, 2 types of adverse events were identified as having special interest in the evaluation of the safety of Tarceva: rash and interstitial lung disease. Therefore, additional analyses were performed for these 2 types of adverse events.

3.4.1.7 Rash

Prior to unblinding of the study, the sponsor defined a term "rash" that encompassed all the appropriate MedDRA rash-related preferred terms. This was done to avoid underestimating the effect of Tarceva by diluting the incidence across multiple preferred terms. In the Tarceva group, 261 patients (60.3%) experienced one or more episodes of "rash" (placebo group 42 patients, 9.4%) and 37 patients (8.5%) had grade 3 "rash"; no grade 4 or 5 "rash" AEs were reported. Two patients experienced serious grade 3 rash.

Two-thirds of the Tarceva-treated patients who experienced rash had it develop within the first 2 weeks of treatment. The protocol included guidelines for the treatment of Tarceva-related rash. The concomitant medications suggested in these guidelines were used more often in the Tarceva group than in the placebo group: corticosteroids (20% vs 7%), tetracycline (15% vs < 1%), antihistamines (12% vs 2%), dermatologic preparations (7% vs 0%), clindamycin (6% versus < 1%), and silver sulfadiazine (1% vs 0%). Despite the high incidence of rash, the rash management guidelines likely had a positive impact on the tolerability as judged by the relatively few dose modifications (8.3%) or discontinuations (1.2%).

3.4.1.7.1 Interstitial Lung Disease

Three patients in the Tarceva group experienced ILD-like events (1 reported as interstitial lung disease diagnosed through chest CT, 1 reported as interstitial pneumonitis diagnosed through chest CT, and 1 reported as mild pulmonary fibrosis diagnosed through chest X-ray) compared with none in the placebo group. All 3 of these events were serious, with 1 case of ILD (onset Day 43) possibly leading to death (investigator ultimately determined cause of death to be due to progressive malignant disease but could not rule out ILD). The other ILD case (onset Day 93) resolved with sequelae, and the pulmonary fibrosis (onset Day 14) was persisting at the time of the patient's death due to progressive malignant disease. Since no lung biopsies were performed on these patients, there was no histological confirmation of ILD.

3.4.1.8 Deaths Due to Adverse Events, and Other Serious Adverse Events

3.4.1.8.1 Deaths

Thirty-five patients (8.1%) in the Tarceva group and 31 patients (7.0%) in the placebo group died during the treatment phase of the study or within 30 days of last study drug dose (26 and 27 due to PD, respectively), as summarized in **Table 3-6**. Among all deaths, investigators determined in the final assessment that 4 in the placebo group and 9 in the Tarceva group were due to an AE. None of these AEs were assessed as causally related to Tarceva by investigators. Nine patients in the Tarceva group died due to events considered unrelated to the study drug by the investigator (cardio-respiratory arrest [2 patients], pneumonia, sudden death, drowning, respiratory failure, cardiac failure, dehydration, and iliac artery thrombosis).

Table 3-6: Summary of Deaths that Ocurred during Treatment Phase

	Tarceva N = 433	**Placebo N = 445**
Total Number of Deaths	35 (8.1%)	31 (7.0%)
Progressive Disease	26* (6.0%)	27 (6.1%)
Adverse Event	9 (2.1%)	4 (0.9%)
Preferred Term:	Cardio-respiratory Arrest (2 patients)	Cardiac Tamponade
	Pneumonia	Empyema
	Sudden Death	Dyspnea
	Drowning	Pulmonary Embolism**
	Respiratory Failure	
	Cardiac Failure	
	Dehydration	
	Iliac Artery Thrombosis	

* One of these patients had grade 5 AE of ILD considered possibly related to study drug.
** Died 22 days after last dose; investigator recorded cause of death as pulmonary embolism but no SAE form was received

An additional 3 patients (1 in the Tarceva group and 2 in the placebo group) had AEs that were reported with a grade 5 (fatal) intensity, although the final investigator assessment was that they died due to progressive disease: ILD in the Tarceva group considered possibly related and hemoptysis and cerebrovascular accident in the placebo group considered unrelated.

The one AE resulting in death that was considered possibly related to Tarceva treatment by the investigator, the investigator ultimately determined that the cause of death was progressive malignant disease, but could not rule out ILD contributing to the death.

3.4.1.8.2 Serious Adverse Events

Forty-seven patients (10.9%) in the Tarceva group experienced at least 1 SAE regardless of causality (placebo: 34 patients, 7.6%). Ten patients in the Tarceva group and 1 in the placebo group experienced SAEs that were regarded by the investigator as related to study treatment. In the Tarceva group, these related SAEs were diarrhea (3 patients), rash (2 patients), ILD (2 patients), pulmonary fibrosis (1 patient), abnormal alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) (1 patient), and respiratory tract infection (1 patient). The nature of these SAEs was consistent with the known safety profile of Tarceva. Most of the Tarceva-related SAEs were manageable by dose modification.

3.4.1.9 Withdrawals and Study Drug Interruptions due to Adverse Events

Twenty patients (4.6%) in the Tarceva group (7 patients, 1.6% in the placebo group) discontinued study medication as a result of an AE. Of these, only the events in 12 patients (2.8%) were considered related to Tarceva: rash (5 patients) diarrhea (2 patients), ILD (2 patients), pulmonary fibrosis, dermatitis acneiform, and fatigue. Other AEs leading to withdrawal but not considered related to Tarceva were gastric perforation, pneumonia, non-cardiac chest pain, dermatitis acneiform, cardio-respiratory arrest (2), urogenital hemorrhage, cardiac failure, dyspnea, and transaminases increased. Thus, AEs leading to withdrawal were consistent with the known safety profile of Tarceva.

In the Tarceva group, 36 patients (8.3%) had dose modifications (interruptions or reductions) due to rash (none in the placebo group), and 14 patients (3.2%) had dose modifications due to diarrhea (1 in the placebo group).

3.4.1.10 Laboratory Abnormalities

Significant laboratory abnormalities (ie, those that had an associated clinical condition, necessitated dose modification or interruption, or met the criteria for a SAE) were reported and analyzed as AEs. The clinical laboratory data obtained from the SATURN study are consistent with laboratory evaluation results observed in previous clinical

studies and are reflected in the current prescribing information. Although grade 1 or 2 blood chemistry laboratory parameter values were common in both treatment groups, grade 3 and 4 were uncommon. There were 10 occurrences of grade 3 liver function test increases in 8 patients. A summary of the liver function test abnormalities is shown in **Table 3-7**.

Table 3-7: Summary of Liver Function Tests – Worst Grade During Treatment

	Grade 1		Grade 2		Grade 3		Grade 4	
	Tarceva	**placebo**	**Tarceva**	**placebo**	**Tarceva**	**placebo**	**Tarceva**	**placebo**
AST*	19.9%	12.6%	2.8%	1.3%	0.5%	0%	0%	0%
ALT*	16.2%	11.2%	2.3%	1.3%	1.2%	0%	0%	0%
Alkaline Phosphatase*	17.6%	19.6%	3.0%	1.8%	0.5%	0.2%	0%	0%
Bilirubin*	11.1%	3.8%	4.4%	0.7%	0.2%	0.4%	0%	0%

* Tarceva: n = 433; placebo: n = 445

The Tarceva group had more patients shift from normal white blood cell count at baseline to grade 1 during the study compared to the placebo group (15 patients vs 9 patients) and for lymphocytes (21 patients vs 8).

Grade 3 and 4 hematology laboratory parameter values were uncommon in both treatment groups. In the Tarceva group, grade 4 hematology laboratory parameter values were limited to 1 patient with grade 4 decreased lymphocytes (grade 1 at baseline). As this patient had an infection with a high WBC count at the time, these are not considered clinical meaningful in the evaluation of the safety of Tarceva.

3.4.2 Safety Conclusions

Tarceva was well tolerated in the SATURN study, with only 11.9% of patients requiring dose reductions and 4.6% permanently discontinuing due to an AE. As expected, rash (60.3% overall) and diarrhea (20.3%) were the most common adverse events and most of these were mild in severity and manageable without dose modifications. Serious adverse events including hospitalization occurred in 10.9% and 7.6% of the patients in the Tarceva and placebo group, respectively. One patient died due to an ILD-like adverse event where a contribution to Tarceva could not be ruled out, although it was confounded by progressive disease.

The safety profile of Tarceva in this study was consistent with that observed in previous clinical studies of single-agent Tarceva in NSCLC and/or during postmarketing

surveillance. There were no new or unexpected safety signals (see Package Insert provided in **Section 6.1**)

4 RISK/BENEFIT DISCUSSION

SATURN was designed to investigate the efficacy and safety of Tarceva in the maintenance setting following response or disease stabilization (ie, CR, PR, or SD and in the absence of unacceptable toxicity) to first-line platinum-based doublet therapy in advanced NSCLC.

SATURN met its co-primary endpoints by demonstrating a statistically significant improvement in investigator-assessed PFS for the overall population (HR = 0.71, $P <$ 0.0001) as well as for patients with EGFR IHC-positive tumors (HR = 0.69; $P < 0.0001$). The robustness and lack of bias of the PFS assessment by the investigator was corroborated by an independent central radiological review. The benefit in PFS correlated with a statistically significant and clinically meaningful benefit in OS in both the overall population and the EGFR IHC-positive population (HR = 0.81, $P = 0.0088$ and HR = 0.77, $P = 0.0063$, respectively, or a 19% and 23% reduction in risk of death, respectively).

Efficacy was shown across study subgroups irrespective of histology, race, gender, smoking status, and ECOG PS. Exploratory analyses among biomarker subgroups indicated that all biomarker subgroups derived benefit. Greatest benefit was observed in the subgroup of patients with EGFR activating mutation, however, significant benefit was also observed in the subgroup with EGFR wildtype.

Tarceva was well tolerated and there were no new or unexpected safety signals. The most common adverse events, rash and diarrhea, can be medically managed. There was no deterioration in quality of life for patients receiving Tarceva when compared with placebo.

The diagnosis of advanced NSCLC is devastating for patients and their families. While first-line platinum-based chemotherapy has improved survival and quality of life for these patients, this therapy is not curative and many patients rapidly progress despite initial benefit. Although second- and third-line therapies have been shown to improve survival, many patients inevitably are not able to receive such therapies due to declining performance status. Approximately 40% of first-line NSCLC patients do not receive

second-line therapy, and approximately 45% of second-line patients do not receive third-line therapy.

Most therapeutics used in the first-line setting of advanced NSCLC are associated with significant toxicities and are administered intravenously, restricting patient quality of life and flexibility during the last months of their lives. After initial benefit from chemotherapy, patients and their families live everyday with the fear of the inevitable progression of their disease and the decline in their performance status. The ability to maintain initial benefit from chemotherapy is a desirable outcome for this population.

While intravenous therapy with pemetrexed was recently FDA approved in the maintenance setting in advanced NSCLC, it is appropriate for only a limited patient population (ie, non-squamous histology). In addition, even in the non-squamous histology subset, not all patients want to continue with an intravenous maintenance therapy due to convenience, toxicity profile, or need to recover from previous chemotherapy. Many patients may prefer a break from chemotherapy as cumulative toxicities mount but may remain interested in considering other therapeutic options to delay disease progression. Thus, the need for a well tolerated, oral agent that can maintain tumor regression gained from initial chemotherapy and prolong the time to progression is a unmet medical need.

Tarceva is a convenient, oral, non-chemotherapy therapeutic option that delays disease progression and prolongs survival with a favorable safety profile in advanced NSCLC patients in the first-line maintenance setting. Tarceva provides physicians and patients with another, much needed, therapeutic option.

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6 APPENDICES

6.1 Tarceva Package Insert

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TARCEVA safely and effectively. See full prescribing information for TARCEVA.

TARCEVA® (erlotinib) tablets, oral
Initial U.S. Approval: 2004

RECENT MAJOR CHANGES

Warnings and Precautions, Gastrointestinal Perforation (5.5)	04/2009
Warnings and Precautions, Bullous Skin Disorders (5.6)	04/2009
Warnings and Precautions, Ocular Disorders (5.10)	04/2009
Warning and Precautions, Renal Failure (5.2)	09/2008
Warnings and Precautions, Hepatotoxicity (5.3)	09/2008
Warnings and Precautions, Hepatic Impairment (5.4)	09/2008

INDICATIONS AND USAGE

TARCEVA is a kinase inhibitor indicated for the treatment of:

- Locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one prior chemotherapy regimen. (1.1)
- First-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine. (1.2)

DOSAGE AND ADMINISTRATION

- The dose for NSCLC is 150 mg/day. (2.1)
- The dose for pancreatic cancer is 100 mg/day. (2.2)
- All doses of TARCEVA should be taken at least one hour before or two hours after food. (2.1, 2.2)
- Reduce in 50 mg decrements, when necessary. (2.3)

DOSAGE FORMS AND STRENGTHS

- Tablets: 25 mg, 100 mg and 150 mg. (3)

CONTRAINDICATIONS

- None. (4)

WARNINGS AND PRECAUTIONS

- Interstitial Lung Disease (ILD)-like events, including fatalities have been infrequently reported. Interrupt TARCEVA if acute onset of new or progressive unexplained pulmonary symptoms, such as dyspnea, cough and fever occur. Discontinue TARCEVA if ILD is diagnosed. (5.1)
- Cases of acute renal failure (including fatalities), and renal insufficiency have been reported. Interrupt TARCEVA in the event of dehydration. Monitor renal function and electrolytes in patients at risk of dehydration. (5.2)
- Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported. Monitor periodic liver function testing. Interrupt or discontinue TARCEVA if liver function changes are severe. (5.3)
- Monitor patients with hepatic impairment closely. Interrupt or discontinue TARCEVA if changes in liver function are severe (5.4)
- Gastrointestinal perforations, including fatalities, have been reported. Discontinue TARCEVA. (5.5)
- Bullous and exfoliative skin disorders, including fatalities, have been reported. Interrupt or discontinue TARCEVA (5.6)
- Myocardial infarction/ischemia has been reported, including fatalities, in patients with pancreatic cancer. (5.7)
- Cerebrovascular accidents, including a fatality, have been reported in patients with pancreatic cancer. (5.8)
- Microangiopathic Hemolytic Anemia with thrombocytopenia has been reported in patients with pancreatic cancer. (5.9)
- Corneal perforation and ulceration have been reported. Interrupt or discontinue TARCEVA (5.10)
- Women should be advised to avoid pregnancy while on TARCEVA. Treatment should only be continued if the potential benefit to the mother outweighs the risk to the fetus. (5.11)
- International Normalized Ratio (INR) elevations and bleeding events, some associated with concomitant warfarin administration have been reported. Monitor patients taking warfarin or other coumarin-derivative anticoagulants. (5.12)

ADVERSE REACTIONS

The most common adverse reactions (>50%) in NSCLC are rash, diarrhea, anorexia and fatigue. (6.1)
The most common adverse reactions (>50%) in pancreatic cancer are fatigue, rash, nausea and anorexia. (6.2)
To report SUSPECTED ADVERSE REACTIONS, contact OSI Pharmaceuticals Inc. at 1-800-572-1932 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch.*

DRUG INTERACTIONS

- CYP3A4 inhibitors may increase erlotinib plasma concentrations. (7)
- CYP3A4 inducers may decrease erlotinib plasma concentrations. (7)
- CYP1A2 inducers may decrease erlotinib plasma concentrations. (7)
- Erlotinib solubility is pH dependent. Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and hence its absorption. (7)
- Cigarette smoking decreases erlotinib plasma concentrations (7)

See 17 for PATIENT COUNSELING INFORMATION.
Revised: [04/2009]

FULL PRESCRIBING INFORMATION: CONTENTS *

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Non-Small Cell Lung Cancer (NSCLC)

TARCEVA monotherapy is indicated for the treatment of patients with locally advanced or metastatic non-small cell lung cancer after failure of at least one prior chemotherapy regimen *[see Clinical Studies (14.1)]*.

Results from two, multicenter, placebo-controlled, randomized, Phase 3 trials conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel or gemcitabine and cisplatin] and its use is not recommended in that setting *[see Clinical Studies (14.3)]*.

1.2 Pancreatic Cancer

TARCEVA in combination with gemcitabine is indicated for the first-line treatment of patients with locally advanced, unresectable or metastatic pancreatic cancer *[see Clinical Studies (14.4)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Dose - NSCLC

The recommended daily dose of TARCEVA for non-small cell lung cancer is 150 mg taken at least one hour before or two hours after the ingestion of food. Treatment should continue until disease progression or unacceptable toxicity occurs. There is no evidence that treatment beyond progression is beneficial.

2.2 Recommended Dose – Pancreatic Cancer

The recommended daily dose of TARCEVA for pancreatic cancer is 100 mg taken at least one hour before or two hours after the ingestion of food, in combination with gemcitabine (see the gemcitabine package insert). Treatment should continue until disease progression or unacceptable toxicity occurs.

2.3 Dose Modifications

In patients who develop an acute onset of new or progressive pulmonary symptoms, such as dyspnea, cough or fever, treatment with TARCEVA should be interrupted pending diagnostic evaluation. If Interstitial Lung Disease (ILD) is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as necessary *[see Warnings and Precautions (5.1)]*. Discontinue TARCEVA for hepatic failure or gastrointestinal perforation. Interrupt or discontinue TARCEVA in patients with dehydration who are at risk for renal failure, in patients with severe bullous, blistering or exfoliative skin conditions, or in patients with acute /worsening ocular disorders *[see Warnings and Precautions (5.3, 5.4, 5.5, 5.6, 5.10)]*.

Diarrhea can usually be managed with loperamide. Patients with severe diarrhea who are unresponsive to loperamide or who become dehydrated may require dose reduction or temporary interruption of therapy. Patients with severe skin reactions may also require dose reduction or temporary interruption of therapy.

When dose reduction is necessary, the TARCEVA dose should be reduced in 50 mg decrements.

In patients who are taking TARCEVA with a strong CYP3A4 inhibitor such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole, or grapefruit or grapefruit juice, a dose reduction should be considered if severe adverse reactions occur. Similarly, in patients who are taking TARCEVA with an inhibitor of both CYP3A4 and CYP1A2 like ciprofloxacin, a dose reduction of TARCEVA should be considered if severe adverse reactions occur *[see Drug Interactions (7)]*.

Pre-treatment with the CYP3A4 inducer rifampicin decreased erlotinib AUC by about 2/3 to 4/5. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, an increase in the dose of TARCEVA should be considered as tolerated at two week intervals while monitoring the patient's safety. The maximum dose of TARCEVA studied in combination with rifampicin is 450 mg. If the TARCEVA dose is adjusted upward, the dose will need to be reduced immediately to the indicated starting dose upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort. These too should be avoided if possible *[see Drug Interactions (7)]*.

Cigarette smoking has been shown to reduce erlotinib exposure. Patients should be advised to stop smoking. If a patient continues to smoke, a cautious increase in the dose of TARCEVA, not exceeding 300 mg may be considered, while monitoring the patient's safety. However, efficacy and long-term safety (> 14 days) of a dose higher than the recommended starting doses have not been established in patients who continue to smoke cigarettes. If the TARCEVA dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking *[see Clinical Pharmacology (12.3)]*.

Erlotinib is eliminated by hepatic metabolism and biliary excretion. Although erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B), patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA [*see Warnings and Precautions (5.4)]*. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range. In the setting of worsening liver function tests, before they become severe, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. TARCEVA dosing should be interrupted or discontinued if total bilirubin is >3 x ULN and/or transaminases are >5 x ULN in the setting of normal pretreatment values *[see Warnings and Precautions (5.3, 5.4), Adverse Reactions (6.3) and Use in Specific Populations (8.6)]*.

3 DOSAGE FORMS AND STRENGTHS

25 mg tablets

White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side.

100 mg tablets

White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side.

150 mg tablets

White film-coated tablets for daily oral administration. Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pulmonary Toxicity

There have been infrequent reports of serious Interstitial Lung Disease (ILD)-like events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors. In the randomized single-agent NSCLC study *[see Clinical Studies (14.1)]*, the incidence of ILD-like events (0.8%) was the same in both the placebo and TARCEVA groups. In the pancreatic cancer study - in combination with gemcitabine – *[see Clinical Studies (14.3)]*, the incidence of ILD-like events was 2.5% in the TARCEVA plus gemcitabine group vs. 0.4% in the placebo plus gemcitabine group.

The overall incidence of ILD-like events in approximately 4900 TARCEVA-treated patients from all studies (including uncontrolled studies and studies with concurrent chemotherapy) was approximately 0.7%. Reported diagnoses in patients suspected of having ILD-like events included pneumonitis, radiation pneumonitis, hypersensitivity pneumonitis, interstitial pneumonia, interstitial lung disease, obliterative bronchiolitis, pulmonary fibrosis, Acute Respiratory Distress Syndrome and lung infiltration. Symptoms started from 5 days to more than 9 months (median 39 days) after initiating TARCEVA therapy. In the lung cancer trials most of the cases were associated with confounding or contributing factors such as concomitant/prior chemotherapy, prior radiotherapy, pre-existing parenchymal lung disease, metastatic lung disease, or pulmonary infections.

In the event of an acute onset of new or progressive unexplained pulmonary symptoms such as dyspnea, cough, and fever, TARCEVA therapy should be interrupted pending diagnostic evaluation. If ILD is diagnosed, TARCEVA should be discontinued and appropriate treatment instituted as needed *[see Dosage and Administration (2.3)]*.

5.2 Renal Failure

Cases of hepatorenal syndrome, acute renal failure (including fatalities), and renal insufficiency have been reported. Some were secondary to baseline hepatic impairment while others were associated with severe dehydration due to diarrhea, vomiting, and/or anorexia or concurrent chemotherapy use. In the event of dehydration, particularly in patients with contributing risk factors for renal failure (eg, pre-existing renal disease, medical conditions or medications that may lead to renal disease, or other predisposing conditions including advanced age), TARCEVA therapy should be interrupted and appropriate measures should be taken to intensively rehydrate the patient. Periodic monitoring of renal function and serum electrolytes is recommended in patients at risk of dehydration *[see Adverse Reactions (6.3) and Dosage and Administration (2.3)]*.

5.3 Hepatotoxicity

Cases of hepatic failure and hepatorenal syndrome (including fatalities) have been reported during use of TARCEVA, particularly in patients with baseline hepatic impairment. Therefore, periodic liver function testing (transaminases, bilirubin, and alkaline phosphatase) is recommended. In the setting of worsening liver function tests, dose interruption and/or dose reduction with frequent liver function test monitoring should be considered. TARCEVA dosing should be interrupted or discontinued if total bilirubin is >3 x ULN and/or transaminases are >5 x ULN in the setting of normal pretreatment values *[see Adverse Reactions (6.3) and Dosage and Administration (2.3)]*.

5.4 Patients with Hepatic Impairment

In a pharmacokinetic study in patients with moderate hepatic impairment (Child-Pugh B) associated with significant liver tumor burden, 10 out of 15 patients died on treatment or within 30 days of the last TARCEVA dose. One patient died from hepatorenal syndrome, 1 patient died from rapidly progressing liver failure and the remaining 8 patients died from progressive disease. Six out of the 10 patients who died had baseline total bilirubin > 3 x ULN suggesting severe hepatic impairment. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN. Patients with hepatic impairment (total bilirubin > ULN or Child-Pugh A, B and C) should be closely monitored during therapy with TARCEVA. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe such as doubling of total bilirubin and/or tripling of transaminases in the setting of pretreatment values outside normal range *[see Clinical Pharmacology (12.3) and Dosage and Administration (2.3)]*.

5.5 Gastrointestinal Perforation

Gastrointestinal perforation (including fatalities) has been reported in patients receiving TARCEVA. Patients receiving concomitant anti-angiogenic agents, corticosteroids, NSAIDs, and/or taxane-based chemotherapy, or who have prior history of peptic ulceration or diverticular disease are at increased risk. *[see Adverse Reactions (6.3]*. Permanently discontinue TARCEVA in patients who develop gastrointestinal perforation.

5.6 Bullous and Exfoliative Skin Disorders

Bullous, blistering and exfoliative skin conditions have been reported including cases suggestive of Stevens-Johnson syndrome/toxic epidermal necrolysis, which in some cases were fatal *[see Adverse Reactions (6.3)]*. Interrupt or discontinue TARCEVA treatment if the patient develops severe bullous, blistering or exfoliating conditions.

5.7 Myocardial infarction/ischemia

In the pancreatic carcinoma trial, six patients (incidence of 2.3%) in the TARCEVA/gemcitabine group developed myocardial infarction/ischemia. One of these patients died due to myocardial infarction. In comparison, 3 patients in the placebo/gemcitabine group developed myocardial infarction (incidence 1.2%) and one died due to myocardial infarction.

5.8 Cerebrovascular accident

In the pancreatic carcinoma trial, six patients in the TARCEVA/gemcitabine group developed cerebrovascular accidents (incidence: 2.3%) One of these was hemorrhagic and was the only fatal event. In comparison, in the placebo/gemcitabine group there were no cerebrovascular accidents.

5.9 Microangiopathic Hemolytic Anemia with Thrombocytopenia

In the pancreatic carcinoma trial, two patients in the TARCEVA/gemcitabine group developed microangiopathic hemolytic anemia with thrombocytopenia (incidence: 0.8%). Both patients received TARCEVA and gemcitabine concurrently. In comparison, in the placebo/gemcitabine group there were no cases of microangiopathic hemolytic anemia with thrombocytopenia.

5.10 Ocular Disorders

Corneal perforation and ulceration have been reported during use of TARCEVA. Other ocular disorders including abnormal eyelash growth, keratoconjunctivitis sicca or keratitis have been observed with TARCEVA treatment and are known risk factors for corneal ulceration/perforation *[see Adverse Reactions (6.3)]*. Interrupt or discontinue TARCEVA therapy if patients present with acute/worsening ocular disorders such as eye pain.

5.11 Use in Pregnancy

Pregnancy Category D

Women of childbearing potential should avoid becoming pregnant while being treated with TARCEVA. Erlotinib administered to rabbits during organogenesis at doses that result in plasma drug concentrations of approximately 3 times those in humans (AUCs at 150 mg daily dose) was associated with embryo/fetal lethality and abortion. When erlotinib was administered to female rats prior to mating and through the first week of pregnancy, at doses 0.3 or 0.7 times the clinical dose of 150 mg, on a mg/m^2 basis, there was an increase in early resorptions that resulted in a decrease in the number of live fetuses *[see Use in Specific Populations (8.1)]*.

5.12 Elevated International Normalized Ratio and Potential Bleeding

International Normalized Ratio (INR) elevations and infrequent reports of bleeding events including gastrointestinal and non-gastrointestinal bleedings have been reported in clinical studies, some associated with concomitant warfarin administration. Patients taking warfarin or other coumarin-derivative anticoagulants should be monitored regularly for changes in prothrombin time or INR *[see Adverse Reactions (6.3)]*.

6 ADVERSE REACTIONS

Because clinical trials are conducted under widely varying conditions, adverse reactions rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Safety evaluation of TARCEVA is based on 856 cancer patients who received TARCEVA as monotherapy, 308 patients who received TARCEVA 100 or 150 mg plus gemcitabine, and 1228 patients who received TARCEVA concurrently with other chemotherapies.

There have been reports of serious events, including fatalities, in patients receiving TARCEVA for treatment of NSCLC, pancreatic cancer or other advanced solid tumors *[see Warnings and Precautions (5) and Dosage and Administration (2.3)]*.

6.1 Non-Small Cell Lung Cancer

Adverse reactions, regardless of causality, that occurred in at least 10% of patients treated with single-agent TARCEVA at 150 mg and at least 3% more often than in the placebo group in the randomized trial of patients with NSCLC are summarized by NCI-CTC (version 2.0) Grade in Table 1.

The most common adverse reactions in patients receiving single-agent TARCEVA 150 mg were rash and diarrhea. Grade 3/4 rash and diarrhea occurred in 9% and 6%, respectively, in TARCEVA-treated patients. Rash and diarrhea each resulted in study discontinuation in 1% of TARCEVA-treated patients. Six percent and 1% of patients needed dose reduction for rash and diarrhea, respectively. The median time to onset of rash was 8 days, and the median time to onset of diarrhea was 12 days.

Table 1: **Adverse Reactions Occurring More Frequently (≥ 3%) in the Single-agent TARCEVA Group than in the Placebo Group and in ≥10% of Patients in the TARCEVA Group.**

	TARCEVA 150 mg N = 485			Placebo N = 242		
NCI-CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Rash	75	8	<1	17	0	0
Diarrhea	54	6	<1	18	<1	0
Anorexia	52	8	1	38	5	<1
Fatigue	52	14	4	45	16	4
Dyspnea	41	17	11	35	15	11
Cough	33	4	0	29	2	0
Nausea	33	3	0	24	2	0
Infection	24	4	0	15	2	0
Vomiting	23	2	<1	19	2	0
Stomatitis	17	<1	0	3	0	0
Pruritus	13	<1	0	5	0	0
Dry skin	12	0	0	4	0	0
Conjunctivitis	12	<1	0	2	<1	0
Keratoconjunctivitis sicca	12	0	0	3	0	0
Abdominal pain	11	2	<1	7	1	<1

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) were observed in patients receiving single-agent TARCEVA 150 mg. These elevations were mainly transient or associated with liver metastases. Grade 2 (>2.5 – 5.0 x ULN) ALT elevations occurred in 4% and <1% of TARCEVA and placebo treated patients, respectively. Grade 3 (>5.0 – 20.0 x ULN) elevations were not observed in TARCEVA-treated patients. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

6.2 Pancreatic Cancer

Adverse reactions, regardless of causality, that occurred in at least 10% of patients treated with TARCEVA 100 mg plus gemcitabine in the randomized trial of patients with pancreatic cancer are summarized by NCI-CTC (version 2.0) Grade in Table 2.

The most common adverse reactions in pancreatic cancer patients receiving TARCEVA 100 mg plus gemcitabine were fatigue, rash, nausea, anorexia and diarrhea. In the TARCEVA plus gemcitabine arm, Grade 3/4 rash and diarrhea were each reported in 5% of TARCEVA plus gemcitabine-treated patients. The median time to onset of rash and diarrhea was 10 days and 15 days, respectively. Rash and diarrhea each resulted in dose reductions in 2% of patients, and resulted in study discontinuation in up to 1% of patients receiving TARCEVA plus gemcitabine. The 150 mg cohort was associated with a higher rate of certain class-specific adverse reactions including rash and required more frequent dose reduction or interruption.

Table 2: **Adverse Reactions Occurring in ≥ 10% of TARCEVA-treated Pancreatic Cancer Patients: 100 mg cohort**

	TARCEVA + Gemcitabine 1000 mg/m² IV N=259			Placebo + Gemcitabine 1000 mg/m² IV N=256		
NCI-CTC Grade	**Any Grade**	**Grade 3**	**Grade 4**	**Any Grade**	**Grade 3**	**Grade 4**
MedDRA Preferred Term	**%**	**%**	**%**	**%**	**%**	**%**
Fatigue	73	14	2	70	13	2
Rash	69	5	0	30	1	0
Nausea	60	7	0	58	7	0
Anorexia	52	6	<1	52	5	<1
Diarrhea	48	5	<1	36	2	0
Abdominal pain	46	9	<1	45	12	<1
Vomiting	42	7	<1	41	4	<1
Weight decreased	39	2	0	29	<1	0
Infection*	39	13	3	30	9	2
Edema	37	3	<1	36	2	<1
Pyrexia	36	3	0	30	4	0
Constipation	31	3	1	34	5	1
Bone pain	25	4	<1	23	2	0
Dyspnea	24	5	<1	23	5	0
Stomatitis	22	<1	0	12	0	0
Myalgia	21	1	0	20	<1	0
Depression	19	2	0	14	<1	0
Dyspepsia	17	<1	0	13	<1	0
Cough	16	0	0	11	0	0
Dizziness	15	<1	0	13	0	<1
Headache	15	<1	0	10	0	0
Insomnia	15	<1	0	16	<1	0
Alopecia	14	0	0	11	0	0
Anxiety	13	1	0	11	<1	0
Neuropathy	13	1	<1	10	<1	0
Flatulence	13	0	0	9	<1	0
Rigors	12	0	0	9	0	0

*Includes all MedDRA preferred terms in the Infections and Infestations System Organ Class

In the pancreatic carcinoma trial, 10 patients in the TARCEVA/gemcitabine group developed deep venous thrombosis (incidence: 3.9%). In comparison, 3 patients in the placebo/gemcitabine group developed deep venous thrombosis (incidence 1.2%). The overall incidence of grade 3 or 4 thrombotic events, including deep venous thrombosis, was similar in the two treatment arms: 11% for TARCEVA plus gemcitabine and 9% for placebo plus gemcitabine.

No differences in Grade 3 or Grade 4 hematologic laboratory toxicities were detected between the TARCEVA plus gemcitabine group compared to the placebo plus gemcitabine group.

Severe adverse reactions (≥grade 3 NCI-CTC) in the TARCEVA plus gemcitabine group with incidences < 5% included syncope, arrhythmias, ileus, pancreatitis, hemolytic anemia including microangiopathic hemolytic anemia with thrombocytopenia, myocardial infarction/ischemia, cerebrovascular accidents including cerebral hemorrhage, and renal insufficiency *[see Warnings and Precautions (5)]*.

Liver function test abnormalities (including elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin) have been observed following the administration of TARCEVA plus gemcitabine in patients with pancreatic cancer. Table 3 displays the most severe NCI-CTC grade of liver function abnormalities that developed. TARCEVA dosing should be interrupted or discontinued if changes in liver function are severe *[see Dosage and Administration (2.3)]*.

Table 3: Liver Function Test Abnormalities (most severe NCI-CTC grade) in Pancreatic Cancer Patients: 100 mg Cohort

	TARCEVA + Gemcitabine 1000 mg/m² IV N = 259			**Placebo + Gemcitabine 1000 mg/m² IV N = 256**		
NCI-CTC Grade	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 2**	**Grade 3**	**Grade 4**
Bilirubin	17 %	10%	<1%	11%	10%	3%
ALT	31%	13%	<1%	22%	9%	0%
AST	24%	10%	<1%	19%	9%	0%

6.3 NSCLC and Pancreatic Cancer Indications

Gastrointestinal Disorders

Gastrointestinal perforations have been reported in patients in clinical studies and during post-marketing use of TARCEVA *[see Warnings and Precautions (5.5)]*.

During the NSCLC and the combination pancreatic cancer trials, infrequent cases of gastrointestinal bleeding have been reported, some associated with concomitant warfarin or NSAID administration *[see Warnings and Precautions (5.12)]*. These adverse reactions were reported as peptic ulcer bleeding (gastritis, gastroduodenal ulcers), hematemesis, hematochezia, melena and hemorrhage from possible colitis.

Renal Disorders

Cases of acute renal failure or renal insufficiency, including fatalities, with or without hypokalemia have been reported *[see Warnings and Precautions (5.2)]*.

Hepatic Disorders

Hepatic failure has been reported in patients treated with single-agent TARCEVA or TARCEVA combined with chemotherapy in clinical studies and during post-marketing use of TARCEVA *[see Warnings and Precautions (5.3)]*; it is not possible to reliably estimate the frequency or establish a causal relationship to TARCEVA treatment.

Ocular Disorders

Corneal ulcerations or perforations have been reported in patients receiving TARCEVA treatment. Abnormal eyelash growth including in-growing eyelashes, excessive growth and thickening of the eyelashes have been reported *[see Warnings and Precautions (5.10)]* and are risk factors for corneal ulceration/perforation.

NCI-CTC Grade 3 conjunctivitis and keratitis have been reported infrequently in patients receiving TARCEVA therapy in the NSCLC and pancreatic cancer clinical trials. Corneal ulcerations may also occur *[see Patient Counseling Information (17)]*.

Skin, Hair and Nail Disorders

Bullous, blistering and exfoliative skin conditions have been reported, including cases suggestive of Stevens-Johnson syndrome/Toxic epidermal necrolysis *[see Warnings and Precautions (5.6)]*.

In patients who develop skin rash, the appearance of the rash is typically erythematous and maculopapular and it may resemble acne with follicular pustules, but is histopathologically different. This skin reaction commonly occurs on the face, upper chest and back, but may be more generalized or severe (NCI-CTC Grade 3 or 4) with desquamation. Skin reactions may occur or worsen in sun exposed areas; therefore, the use of sunscreen or avoidance of sun exposure is recommended. Associated symptoms may include itching, tenderness and/or burning. Also, hyperpigmentation or dry skin with or without digital skin fissures may occur.

Hair and nail disorders including alopecia, hirsutism, eyelash/eyebrow (see above) changes, paronychia and brittle and loose nails have been reported in clinical trials and during post-marketing use of TARCEVA.

Other Disorders

Epistaxis has been reported in both the single-agent NSCLC and the pancreatic cancer clinical trials.

In general, no notable differences in the safety of TARCEVA monotherapy or in combination with gemcitabine could be discerned between females or males and between patients younger or older than the age of 65 years *[see Use in SpecificPopulations (8.4)]*. The safety of TARCEVA appears similar in Caucasian and Asian patients.

7 DRUG INTERACTIONS

Erlotinib is metabolized predominantly by CYP3A4, and inhibitors of CYP3A4 would be expected to increase exposure. Co-treatment with the potent CYP3A4 inhibitor ketoconazole increases erlotinib AUC by 2/3. When TARCEVA was co-administered with ciprofloxacin, an inhibitor of both CYP3A4 and CYP1A2, the erlotinib exposure [AUC] and maximum concentration [C_{max}] increased by 39% and 17% respectively. Caution should be used when administering or taking TARCEVA with ketoconazole and other strong CYP3A4 inhibitors such as, but not limited to, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, troleandomycin (TAO), voriconazole and grapefruit or grapefruit juice *[see Dosage and Administration (2.3)]*.

Pre-treatment with the CYP3A4 inducer rifampicin for 7 days prior to TARCEVA decreased erlotinib AUC by about 2/3 to 4/5, which is equivalent to a dose of about 30 to 50 mg in NSCLC patients. In a separate study, treatment with rifampicin for 11 days, with co-administration of a single 450 mg dose of TARCEVA on day 8 resulted in a mean erlotinib exposure (AUC) that was 57.6% of that observed following a single 150 mg TARCEVA dose in the absence of rifampicin treatment *[see Dose Modifications (2.3)]*. Use of alternative treatments lacking CYP3A4 inducing activity is strongly recommended. If an alternative treatment is unavailable, adjusting the starting dose should be considered. If the TARCEVA dose is adjusted upward, the dose will need to be reduced immediately to the indicated starting dose upon discontinuation of rifampicin or other inducers. Other CYP3A4 inducers include, but are not limited to, rifabutin, rifapentine, phenytoin, carbamazepine, phenobarbital and St. John's Wort *[see Dosage and Administration (2.3)]*.

Cigarette smoking has been shown to reduce erlotinib AUC. Patients should be advised to stop smoking; however, if they continue to smoke, cautious increase in the dose of TARCEVA may be considered, while monitoring the patient's safety. If the TARCEVA dose is adjusted upward, the dose should be reduced immediately to the indicated starting dose upon cessation of smoking *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

Pretreatment and co-administration of TARCEVA decreased the AUC of CYP3A4 substrate, midazolam, by 24%. The mechanism is not clear.

In a study, there were no significant effects of gemcitabine on the pharmacokinetics of erlotinib nor were there significant effects of erlotinib on the pharmacokinetics of gemcitabine.

Drugs that alter the pH of the upper GI tract may alter the solubility of erlotinib and reduce its bioavailability. Co-administration of TARCEVA with omeprazole, a proton pump inhibitor, decreased the erlotinib AUC by 46%. Increasing the dose of TARCEVA when co-administered with such agents is not likely to compensate for the loss of exposure. Since proton pump inhibitors affect pH of the upper GI tract for an extended period, separation of doses may not eliminate the interaction. The concomitant use of proton pump inhibitors with TARCEVA should be avoided if possible. The use of antacids may be considered in place of histamine 2 receptor blockers (H_2 blockers) or proton pump inhibitors in patients receiving TARCEVA. However, no clinical study has been conducted to evaluate the effect of antacids on erlotinib pharmacokinetics. If an antacid is necessary, the antacid dose and the TARCEVA dose should be separated by several hours *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category D *[See Warnings and Precautions (5.11)]*

Erlotinib has been shown to cause maternal toxicity with associated embryo/fetal lethality and abortion in rabbits when given at doses that result in plasma drug concentrations of approximately 3 times those in humans (AUCs at 150 mg daily dose). When given during the period of organogenesis to achieve plasma drug concentrations approximately equal to those in humans, based on AUC, there was no increased incidence of embryo/fetal lethality or abortion in rabbits or rats. However, female rats treated with 30 mg/m^2/day or 60 mg/m^2/day (0.3 or 0.7 times the clinical dose, on a mg/m^2 basis) of erlotinib prior to mating through the first week of pregnancy had an increase in early resorptions that resulted in a decrease in the number of live fetuses.

No teratogenic effects were observed in rabbits or rats dosed with erlotinib during organogenesis at doses up to 600 mg/m^2/day in the rabbit (3 times the plasma drug concentration seen in humans at 150 mg/day) and up to 60 mg/m^2/day in the rat (0.7 times the clinical dose of 150 mg/day on a mg/m^2 basis).

There are no adequate and well-controlled studies in pregnant women using TARCEVA. Women of childbearing potential should be advised to avoid pregnancy while on TARCEVA. Adequate contraceptive methods should be used during therapy, and for at least 2 weeks after completing therapy. Treatment should only be continued in pregnant women if the potential benefit to the mother outweighs the risk to the fetus. If TARCEVA is used during pregnancy, the patient should be apprised of the potential hazard to the fetus or potential risk for loss of the pregnancy *[see Warnings and Precautions (5.11)]*.

8.3 Nursing Mothers

It is not known whether erlotinib is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from TARCEVA, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The safety and effectiveness of TARCEVA in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients participating in the randomized NSCLC trial, 62% were less than 65 years of age, and 38% of patients were aged 65 years or older. The survival benefit was maintained across both age groups [HR = 0.75 (95% CI: 0.6, 0.9) in patients less than 65 years of age, and HR = 0.79 ((5% CI: 0.6, 1.0) in patients who were 65 years or older].

In the pancreatic cancer study, 53% of patients were younger than 65 years of age and 47% were 65 years of age or older. There were no clinically relevant differences between the age groups [HR = 0.78 (95% CI: 0.6, 1.0) in patients less than 65 years of age, and HR = 0.94 (95% CI: 0.7, 1.2) in patients who were

65 years or older]. No meaningful differences in safety or pharmacokinetics were observed between younger and older patients in either study. Therefore, no dosage adjustments are recommended in elderly patients.

8.6 Gender

Of the total number of patients participating in the randomized NSCLC trial, 65% were males and 35% females. There were no clinically relevant differences in safety and efficacy based on gender [HR = 0.76 (95% CI: 0.6, 0.9) in males and HR = 0.80 (95% CI: 0.6, 1.1) in females].

In the pancreatic cancer study, 52% of patients were males and 48% females. There were no clinically relevant differences in safety and efficacy based on gender [HR = 0.74 (95% CI: 0.6, 0.9) in males and HR = 1.0 (95% CI: 0.8, 1.3) in females].

8.7 Race

In the randomized NSCLC trial, 78% of all patients were Caucasian and 12% were Asian. There were no clinically relevant differences in safety and efficacy based on race [HR = 0.79 (95% CI: 0.6, 1.0) in Caucasians and HR = 0.61 (95% CI: 0.4, 1.0) in Asians].

In the pancreatic cancer study, 88% of all patients were Caucasian and 7% were Asian. There were no clinically relevant differences in safety and efficacy based on race [HR = 0.88 (95% CI: 0.7, 1.1) in Caucasians and HR = 0.61 (95% CI: 0.3, 1.3) in Asians].

8.8 Patients with Hepatic Impairment

Patients with hepatic impairment (total bilirubin > ULN or Child Pugh A, B and C) should be closely monitored during therapy with TARCEVA. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN *[see Warnings (5.4), Adverse Reactions (6.3), and Dosage and Administration (2.3)]*.

In vitro and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver. However, erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases *[see Dosage and Administration (2.3) and Clinical Pharmacology (12.3)]*.

8.9 Patients with Renal Impairment

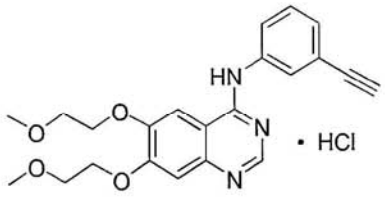
Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

10 OVERDOSAGE

Single oral doses of TARCEVA up to 1,000 mg in healthy subjects and weekly doses up to 1,600 mg in cancer patients have been tolerated. Repeated twice-daily doses of 200 mg single-agent TARCEVA in healthy subjects were poorly tolerated after only a few days of dosing. Based on the data from these studies, an unacceptable incidence of severe adverse reactions, such as diarrhea, rash, and liver transaminase elevation, may occur above the recommended dose *[see Dosage and Administration (2)]*. In case of suspected overdose, TARCEVA should be withheld and symptomatic treatment instituted.

11 DESCRIPTION

TARCEVA (erlotinib),a kinase inhibitor, is a quinazolinamine with the chemical name N-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)-4-quinazolinamine. TARCEVA contains erlotinib as the hydrochloride salt that has the following structural formula:



Erlotinib hydrochloride has the molecular formula $C_{22}H_{23}N_3O_4.HCl$ and a molecular weight of 429.90. The molecule has a pK_a of 5.42 at 25°C. Erlotinib hydrochloride is very slightly soluble in water, slightly soluble in methanol and practically insoluble in acetonitrile, acetone, ethyl acetate and hexane.

Aqueous solubility of erlotinib hydrochloride is dependent on pH with increased solubility at a pH of less than 5 due to protonation of the secondary amine. Over the pH range of 1.4 to 9.6, maximal solubility of approximately 0.4 mg/mL occurs at a pH of approximately 2.

TARCEVA tablets for oral administration are available in three dosage strengths containing erlotinib hydrochloride (27.3 mg, 109.3 mg and 163.9 mg) equivalent to 25 mg, 100 mg and 150 mg erlotinib and the following inactive ingredients: lactose monohydrate, hypromellose, hydroxypropyl cellulose, magnesium stearate, microcrystalline cellulose, sodium starch glycolate, sodium lauryl sulfate and titanium dioxide. The tablets also contain trace amounts of color additives, including FD&C Yellow #6 (25 mg only) for product identification.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The mechanism of clinical antitumor action of erlotinib is not fully characterized. Erlotinib inhibits the intracellular phosphorylation of tyrosine kinase associated with the epidermal growth factor receptor (EGFR). Specificity of inhibition with regard to other tyrosine kinase receptors has not been fully characterized. EGFR is expressed on the cell surface of normal cells and cancer cells.

12.3 Pharmacokinetics

Absorption and Distribution:

Erlotinib is about 60% absorbed after oral administration and its bioavailability is substantially increased by food to almost 100%. Peak plasma levels occur 4 hours after dosing. The solubility of erlotinib is pH dependent. Erlotinib solubility decreases as pH increases. Co-administration of TARCEVA with omeprazole, a proton pump inhibitor, decreased the erlotinib exposure [AUC] and maximum concentration [C_{max}] by 46% and 61% respectively *[see Drug Interactions (7)]*.

Following absorption, erlotinib is approximately 93% protein bound to plasma albumin and alpha-1 acid glycoprotein (AAG). Erlotinib has an apparent volume of distribution of 232 liters.

Metabolism and Excretion:

A population pharmacokinetic analysis in 591 patients receiving single-agent TARCEVA showed a median half-life of 36.2 hours. Time to reach steady state plasma concentration would therefore be 7 – 8 days. No significant relationships of clearance to covariates of patient age, body weight or gender were observed. Smokers had a 24% higher rate of erlotinib clearance.

A second population pharmacokinetic analysis was conducted that incorporated erlotinib data from 204 pancreatic cancer patients who received erlotinib plus gemcitabine. This analysis demonstrated that covariates affecting erlotinib clearance in patients from the pancreatic study were very similar to those seen in the prior single-agent pharmacokinetic analysis. No new covariate effects were identified. Co-administration of gemcitabine had no effect on erlotinib plasma clearance.

In vitro assays of cytochrome P450 metabolism showed that erlotinib is metabolized primarily by CYP3A4 and to a lesser extent by CYP1A2, and the extrahepatic isoform CYP1A1. Following a 100 mg oral dose, 91% of the dose was recovered: 83% in feces (1% of the dose as intact parent) and 8% in urine (0.3% of the dose as intact parent).

Cigarette smoking reduces erlotinib exposure. In the Phase 3 NSCLC trial, current smokers achieved erlotinib steady-state trough plasma concentrations which were approximately 2-fold less than the former smokers or patients who had never smoked. This effect was accompanied by a 24% increase in apparent erlotinib plasma clearance. In a separate study which evaluated the single-dose pharmacokinetics of erlotinib in healthy volunteers, current smokers cleared the drug faster than former smokers or volunteers who had never smoked. The $AUC_{0\text{-infinity}}$ in smokers was about 1/3 to 1/2 of that in never/former smokers. In another study which was conducted in NSCLC patients (N=35) who were current smokers, pharmacokinetic analyses at steady-state indicated a dose-proportional increase in erlotinib exposure when the TARCEVA dose was increased from 150 mg to 300 mg. However, the exact dose to be recommended for patients who currently smoke is unknown *[see Drug Interactions (7) and Patient Counseling Information (17)]*.

Special Populations:

Patients with Hepatic Impairment

Patients with hepatic impairment (total bilirubin > ULN or Child Pugh A, B and C) should be closely monitored during therapy with TARCEVA. Treatment with TARCEVA should be used with extra caution in patients with total bilirubin > 3 x ULN *[see Warnings and Precautions (5.4), Adverse Reactions (6.3), and Dosage and Administration (2.3)]*.

In vitro and *in vivo* evidence suggest that erlotinib is cleared primarily by the liver. However, erlotinib exposure was similar in patients with moderately impaired hepatic function (Child-Pugh B) compared with patients with adequate hepatic function including patients with primary liver cancer or hepatic metastases.

Patients with Renal Impairment

Less than 9% of a single dose is excreted in the urine. No clinical studies have been conducted in patients with compromised renal function.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Erlotinib has not been tested for carcinogenicity.

Erlotinib has been tested for genotoxicity in a series of *in vitro* assays (bacterial mutation, human lymphocyte chromosome aberration, and mammalian cell mutation) and an *in vivo* mouse bone marrow micronucleus test and did not cause genetic damage.

Erlotinib did not impair fertility in either male or female rats.

14 CLINICAL STUDIES

14.1 Non-Small Cell Lung Cancer (NSCLC) – TARCEVA Administered as a Single-agent

The efficacy and safety of single-agent TARCEVA was assessed in a randomized, double blind, placebo-controlled trial in 731 patients with locally advanced or metastatic NSCLC after failure of at least one chemotherapy regimen. Patients were randomized 2:1 to receive TARCEVA 150 mg or placebo (488 Tarceva, 243 placebo) orally once daily until disease progression or unacceptable toxicity. Study endpoints included overall survival, response rate, and progression-free survival (PFS). Duration of response was also examined. The primary endpoint was survival. The study was conducted in 17 countries.

Table 4 summarizes the demographic and disease characteristics of the study population. Demographic characteristics were well balanced between the two treatment groups. About two-thirds of the patients were male. Approximately one-fourth had a baseline ECOG performance status (PS) of 2, and 9% had a baseline ECOG PS of 3. Fifty percent of the patients had received only one prior regimen of chemotherapy. About three quarters of these patients were known to have smoked at some time.

Table 4: Demographic and Disease Characteristics

	TARCEVA (N = 488)		**Placebo (N = 243)**	
Characteristics	**N**	**(%)**	**N**	**(%)**
Gender				
Female	173	(35)	83	(34)
Male	315	(65)	160	(66)

Age (years)				
< 65	299	(61)	153	(63)
≥ 65	189	(39)	90	(37)
Race				
Caucasian	379	(78)	188	(77)
Black	18	(4)	12	(5)
Asian	63	(13)	28	(12)
Other	28	(6)	15	(6)
ECOG Performance Status at Baseline*				
0	64	(13)	34	(14)
1	256	(52)	132	(54)
2	126	(26)	56	(23)
3	42	(9)	21	(9)
Weight Loss in Previous 6 Months				
< 5%	320	(66)	166	(68)
5 – 10%	96	(20)	36	(15)
> 10%	52	(11)	29	(12)
Unknown	20	(4)	12	(5)
Smoking History				
Never Smoked	104	(21)	42	(17)
Current or Ex-smoker	358	(73)	187	(77)
Unknown	26	(5)	14	(6)
Histological Classification				
Adenocarcinoma	246	(50)	119	(49)
Squamous	144	(30)	78	(32)
Undifferentiated Large Cell	41	(8)	23	(9)
Mixed Non-Small Cell	11	(2)	2	(<1)
Other	46	(9)	21	(9)
Time from Initial Diagnosis to Randomization (Months)				
< 6	63	(13)	34	(14)
6 – 12	157	(32)	85	(35)
> 12	268	(55)	124	(51)
Best Response to Prior Therapy at				

Baseline*				
CR/PR	196	(40)	96	(40)
PD	101	(21)	51	(21)
SD	191	(39)	96	(40)
Number of Prior Regimens at Baseline*				
1	243	(50)	121	(50)
2	238	(49)	119	(49)
3	7	(1)	3	(1)
Exposure to Prior Platinum at Baseline*				
Yes	454	(93)	224	(92)
No	34	(7)	19	(8)

* Stratification factor as documented at baseline; distribution differs slightly from values reported at time of randomization.

The results of the study are shown in Table 5.

Table 5: Efficacy Results

	TARCEVA	**Placebo**	**Hazard Ratio (1)**	**95% CI**	**p-value**
Survival	Median 6.7 mo	Median 4.7 mo	0.73	0.61 – 0.86	<0.001 (2)
1-year Survival	31.2%	21.5%			
Progression-Free Survival	Median 9.9 wk	Median 7.9 wk	0.59	0.50 – 0.70	<0.001 (2)
Tumor Response (CR+PR)	8.9%	0.9%			<0.001 (3)
Response Duration	Median 34.3 wk	Median 15.9 wk			

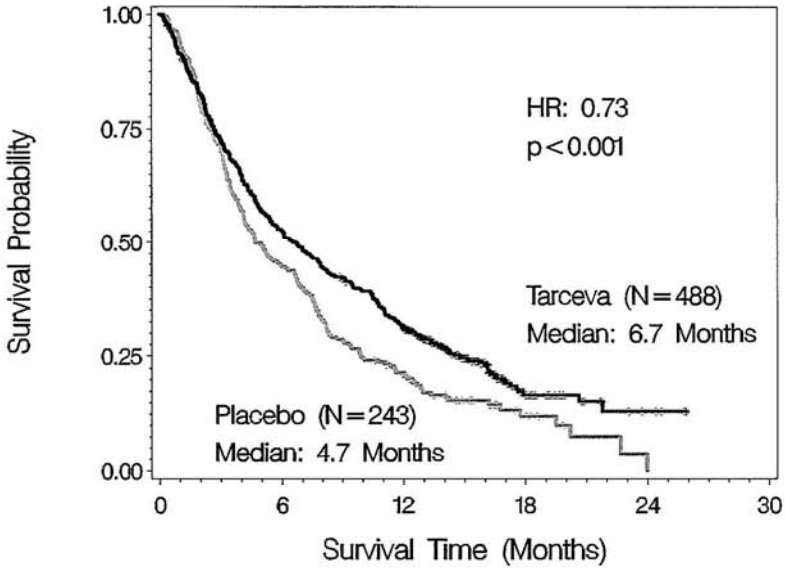
(1) Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

(2) Two-sided Log-Rank test stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

(3) Two-sided Fisher's exact test

Survival was evaluated in the intent-to-treat population. Figure 1 depicts the Kaplan-Meier curves for overall survival. The primary survival and PFS analyses were two-sided Log-Rank tests stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

Figure 1: Kaplan–Meier Curve for Overall Survival of Patients by Treatment Group



Note: HR is from Cox regression model with the following covariates: ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy. P-value is from two-sided Log-Rank test stratified by ECOG performance status, number of prior regimens, prior platinum, best response to prior chemotherapy.

14.2 NSCLC - TARCEVA Administered Concurrently with Chemotherapy

Results from two, multicenter, placebo-controlled, randomized, trials in over 1000 patients conducted in first-line patients with locally advanced or metastatic NSCLC showed no clinical benefit with the concurrent administration of TARCEVA with platinum-based chemotherapy [carboplatin and paclitaxel (TARCEVA, N = 526) or gemcitabine and cisplatin (TARCEVA, N = 580)].

14.3 Pancreatic Cancer - TARCEVA Administered Concurrently with Gemcitabine

The efficacy and safety of TARCEVA in combination with gemcitabine as a first-line treatment was assessed in a randomized, double blind, placebo-controlled trial in 569 patients with locally advanced, unresectable or metastatic pancreatic cancer. Patients were randomized 1:1 to receive TARCEVA (100 mg or 150 mg) or placebo once daily on a continuous schedule plus gemcitabine IV (1000 mg/m^2, Cycle 1 - Days 1, 8, 15, 22, 29, 36 and 43 of an 8 week cycle; Cycle 2 and subsequent cycles - Days 1, 8 and 15 of a 4 week cycle [the approved dose and schedule for pancreatic cancer, see the gemcitabine package insert]). TARCEVA or placebo was taken orally once daily until disease progression or unacceptable toxicity. The primary endpoint was survival. Secondary endpoints included response rate, and progression-free survival (PFS). Duration of response was also examined. The study was conducted in 18 countries. A total of 285 patients were randomized to receive gemcitabine plus TARCEVA (261 patients in the 100 mg cohort and 24 patients in the 150 mg cohort) and 284 patients were randomized to receive gemcitabine plus placebo (260 patients in the 100 mg cohort and 24 patients in the 150 mg cohort). Too few patients were treated in the 150 mg cohort to draw conclusions.

Table 6 summarizes the demographic and disease characteristics of the study population that was randomized to receive 100 mg of TARCEVA plus gemcitabine or placebo plus gemcitabine. Baseline demographic and disease characteristics of the patients were similar between the 2 treatment groups, except for a slightly larger proportion of females in the TARCEVA arm (51%) compared with the placebo arm (44%). The median time from initial diagnosis to randomization was approximately 1.0 month. Most patients presented with metastatic disease at study entry as the initial manifestation of pancreatic cancer.

Table 6: Demographic and Disease Characteristics: 100 mg Cohort

	TARCEVA+ Gemcitabine (N=261)		Placebo + Gemcitabine (N=260)	
Characteristics	**N**	**(%)**	**N**	**(%)**
Gender				
Female	134	(51)	114	(44)
Male	127	(49)	146	(56)
Age (Years)				
<65	136	(52)	138	(53)
≥65	125	(48)	122	(47)
Race				
Caucasian	225	(86)	231	(89)
Black	8	(3)	5	(2)
Asian	20	(8)	14	(5)
Other	8	(3)	10	(3)
ECOG Performance Status*				
0	82	(31)	83	(32)
1	134	(51)	132	(51)
2	44	(17)	45	(17)
Unknown*	1	(<1)	0	(0)
Disease Status at Baseline**				
Locally Advanced	61	(23)	63	(24)
Distant Metastasis	200	(77)	197	(76)

*Unknown includes responses of 'Unknown' and missing.

**Stratification factor as documented at baseline; distribution differs slightly from values reported at time of randomization.

The results of the study are shown in Table 7.

Table 7: Efficacy Results: 100 mg Cohort

	TARCEVA + Gemcitabine	Placebo+ Gemcitabine	Hazard Ratio (1)	95% CI	p-value
Survival	Median 6.4 mo 250 deaths	Median 6.0 mo 254 deaths	0.81	0.68 – 0.97	0.028 (2)
1-year Survival	23.8%	19.4%			
Progression-Free Survival	Median 3.8 mo 225 events	Median 3.5 mo 232 events	0.76	0.64 – 0.92	0.006 (2)
Tumor Response (CR+PR)	8.6%	7.9%			0.87 (3)
Response Duration	Median 23.9 wk	Median 23.3 wk			

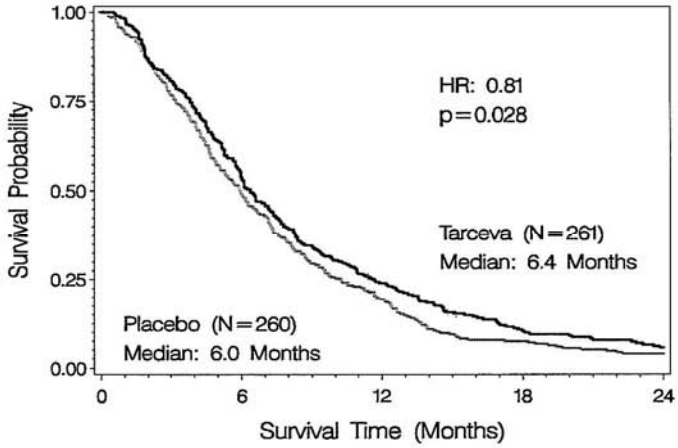
(1) Cox regression model with the following covariates: ECOG performance status, and extent of disease.

(2) Two-sided Log-Rank test stratified by ECOG performance status and extent of disease.

(3) Two-sided Fisher's exact test.

Survival was evaluated in the intent-to-treat population. Figure 2 depicts the Kaplan-Meier curves for overall survival in the 100 mg cohort. The primary survival and PFS analyses were two-sided Log-Rank tests stratified by ECOG performance status and extent of disease.

Figure 2: Kaplan – Meier Curve for Overall Survival: 100 mg Cohort



Note: HR is from Cox regression model with the following covariates: ECOG performance status and extent of disease. P-value is from two-sided Log-Rank test stratified by ECOG performance status and extent of disease.

16 HOW SUPPLIED/STORAGE AND HANDLING

25 mg Tablets

Round, biconvex face and straight sides, white film-coated, printed in orange with a "T" and "25" on one side and plain on the other side; supplied in:

Bottles of 30: NDC 50242-062-01

100 mg Tablets

Round, biconvex face and straight sides, white film-coated, printed in gray with "T" and "100" on one side and plain on the other side; supplied in:
Bottles of 30: NDC 50242-063-01

150 mg Tablets
Round, biconvex face and straight sides, white film-coated, printed in maroon with "T" and "150" on one side and plain on the other side; supplied in:
Bottles of 30: NDC 50242-064-01

Store at 25°C (77°F); excursions permitted to 15° – 30°C (59° – 86°F). See USP Controlled Room Temperature.

17 PATIENT COUNSELING INFORMATION

If the following signs or symptoms occur, patients should be advised to seek medical advice promptly *[see Warnings and Precautions (5), Adverse Reactions (6) and Dosage and Administration (2.3)]*.

- Onset or worsening of skin rash
- Severe or persistent diarrhea, nausea, anorexia, or vomiting
- Onset or worsening of unexplained shortness of breath or cough
- Eye irritation

Given that skin reactions are anticipated when taking TARCEVA, proactive intervention may include alcohol-free emollient cream and use of sunscreen or avoidance of sun exposure *[see Adverse Reactions (6.3).]* The management of rash should be discussed with the patient. This may include topical corticosteroids or antibiotics with anti-inflammatory properties. These approaches were used in the NSCLC and pancreatic pivotal clinical trials. Acne preparations with drying properties may aggravate the dry skin and erythema. Treatment of rash has not been formally studied and should be based on rash severity.

Women of childbearing potential should be advised to avoid becoming pregnant while taking TARCEVA *[see Warnings and Precautions (5.11) and Use in Specific Populations (8.1)]*.

Smokers should be advised to stop smoking while taking TARCEVA as plasma concentrations of erlotinib are reduced due to the effect of cigarette smoking *[see Clinical Pharmacology (12.3)]*.

Manufactured for:

OSI Pharmaceuticals Inc., Melville, NY 11747

Manufactured by:

Schwarz Pharma Manufacturing, Seymour, IN 47274

Distributed by:

Genentech USA, Inc. 1 DNA Way, South San Francisco, CA 94080-4990

For further information please call 1-877-TARCEVA (1-877-827-2382).

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